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Chemicals Which Have Been Tested for Neurotoxic Effects

Tracor Jitco, Inc.

Prepared For
Environmental Protection Agency

May 1976

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CHEMICALS WHICH HAVE BEEN TESTED FOR NEUROTOXIC EFFECTS

MAY 1976

FINAL REPORT

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C.

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16. ABSTRACT

An extensive literature search was conducted to prepare this catalog of chemicals which have been tested for neurotoxic effects. The text of the catalog consists of a series of brief extracts of the experimental procedures and findings of studies in which chemicals were tested for neurotoxic effects. The document is indexed by chemical, class of chemical, and selected neurotoxic effects.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Neurotoxic chemicals Neurotoxic effects Neurotoxicity		

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CHEMICALS WHICH HAVE BEEN TESTED FOR NEUROTOXIC EFFECTS

Final Report

May 1976

Contract 68-01-3255, Task 4

Office of Toxic Substances
Environmental Protection Agency
Washington, D.C. 20460

Frank Letkiewicz

Project Officer

NOTICE

This report has been reviewed by the Office of Toxic Substances, EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade names or commercial products constitute indorsement or recommendation for use.

PREFACE

This document presents information obtained from the literature on substances that have been tested for neurotoxic effects. Damage to the central and/or peripheral nervous systems is an important category of hazards from chemicals that enter the human environment. A variety of chemicals are known to be neurotoxic and there are many reported incidents of chemically induced neurotoxicity in humans. However, this category of hazards has received far less attention than other hazards such as cancer and birth defects.

Recognizing this, the office of Toxic Substances (OTS) initiated a task to collect reports of chemicals tested for neurotoxic activity published in the scientific literature. One intention of this task was to develop a data base which could be utilized by the Office of Toxic Substances in developing techniques for correlating reported effects (in this case neurotoxic effects) of substances with their chemical and/or physical properties. At the same time, it was recognized that the data base developed would be the first such compilation of information, and, as such, could find use among other persons or organizations concerned with adverse health effects induced by chemicals. Therefore, it was decided that the collected data should be made available through publication. It should be noted that reports of tests for neurotoxic effects yielding both positive and negative findings were extracted for this document.

For the purpose of this task, neurotoxic effects are defined as structural or functional damage to the nervous system, such as, histological changes in nerve tissue, grossly observable dysfunction (e.g., paralysis), instrumentally detectable dysfunction (e.g. electroencephalographic changes), and performance dysfunction (e.g., using the rotating rod test for balance). Qualitative effects such as hallucinations or mental depression were also included in the case of reports on humans. Teratological findings affecting the offspring of pregnant females exposed to chemical substances were included. Biochemical disturbances in the nervous systems produced by chemical substances were generally not included; some exceptions are: inhibition of the enzyme cholinesterase and other esterases present in the nervous system, GABA levels, and serotonin levels.

Problems of terminology were met in the literature at every stage of the task. Technical terms were found to be used in different senses, often imprecisely, so that the degree and often the type of dysfunction was difficult to infer from many of the reports. In such cases it was impossible to modify the terms to conform to a meaningful, consistent nomenclature. Thus, the descriptive medical terms used in the extracts are generally the authors' own.

This problem was most apparent in the literature search. Most of the secondary sources are not indexed by general terms for neurotoxicity. It was necessary, therefore, to perform much of the literature searching by scanning primary publications directly. Practical constraints resulted in the ability to scan only select journals, and many of those only for select years of publication. However, the selection of journals and other sources searched provided for a reasonably thorough coverage of the subject. The sources employed in the literature search are listed in the appendix.

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Introduction

The text of this document consists of a series of brief extracts of studies in which chemicals were tested for neurotoxic effects. A separate extract was prepared for each chemical reported in each article. The extracts, which are arranged in alphabetical order by subject chemical, are a structured arrangement of data as presented in the original articles. Each review contains, if it was available, the following information:

Compound: the subject chemical of the study. The chemical nomenclature used is that established by the Chemical Abstracts Service for their 8th Collective Index.

Reference: a complete bibliographic citation, consisting of author(s), journal, volume, issue, pages and year of publication.

Observed neurotoxic effects: reported dysfunctions and structural changes of the nervous system effected by exposure to the subject compounds.

Animals: species, variety, age, sex, and weight of the test animals.

Preparation and Dose or History of Patient: preliminary treatment of test animals, quantity of compound administered, and duration of exposure.

Route and Site: method and location of administration of the compound.

Control Information: preparation and treatment of control animals.

Duration of experiment: period of time during which the test animals were observed.

Exam. Type: general technical procedures employed in the study.

The following is a list of the abbreviations used in the extracts.

atm - atmosphere

av - average

CD_{50} - the dose which was calculated to cause convulsions in 50% of the animals

cmpd - compound

CNS - central nervous system

d - day

ED_{50} - the dose which was calculated to be effective for 50% of the animals for the test employed

F - female

g - gram

GABA - gamma-aminobutyric acid

grp - group

inj - injection

I.P. - intraperitoneal

I.Tub. - intubation

IU - international unit

I.V. - intravenous

kg - kilogram

LD_{50} - the dose which was calculated to be lethal to 50% of the animals

M - male; mole

MAC - Maximum acceptable concentration

mcCi - microcurie

mcg - microgram

mEq - milliequivalent

mg - milligram

min - minute

ml - milliliter

mM - millimole

mo - month

ns - not stated

PNS - peripheral nervous system

P.O. - per os

ppm - parts per million

sacr. - sacrificed

S.C. - subcutaneous

sec - second

soln - solution

TLV - threshold limit value

trtd - treated

untrtd - untreated

wk - week

w/v - weight/volume

yr - year

An index has been prepared to facilitate the use of this document. To locate a compound in the text, one should first look it up in the index. The index will identify the page(s) of the text dealing with the compound. It will also identify the class of chemical, selected neurotoxic effects induced by the chemical, and reported human exposure to the chemical. The index can also be used to identify the chemicals in a given class, chemicals which induce selected neurotoxic effects, and chemicals for which incidents or studies involving humans have been reported.

COMPOUND: Acetaldehyde

000075070

REFERENCE: Schneider, F.H.
Biochem. Pharm. 23:223-229, 1974.

OBSERVED NEUROTOXIC EFFECTS: Total catecholamines expressed as micromoles of epinephrine. Rate of release increased with time of exposure to acetaldehyde; concentration-response curve shifted to left with acetaldehyde but not with carbachol. When conc. of acetaldehyde was lowered below 2×10^{-3} M, delay of peak response increased. Withdrawal of acetaldehyde returned catecholamine levels to normal.

ANIMALS: Bovine adrenals in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: Adrenals 10-20 g perfused with Tyrode soln at 37° containing acetaldehyde at 1.5×10^{-3} to 2.5×10^{-2} M. Perfusate was analyzed for total catecholamines.

ROUTE AND SITE: Perfusion was retrograde via adrenal vein, at 10 ml/min.

CONTROL INFORMATION: Some adrenals were perfused with carbachol.

DURATION OF EXPERIMENT: About 2 hr.

EXAM. TYPE: Biochemical

COMPOUND: Acetaldehyde, chloro-, (2,4-dinitrophenyl) hydrazone

005135808

REFERENCE: Ambrose, A.M., Borzelleca, J.F., Larson, P.S., Smith, R.B., Jr., and Hennigar, G.R.
Tox. Appl. Pharm. 8:472-481, 1966.

OBSERVED NEUROTOXIC EFFECTS: Subacute: 1500 and higher levels, hindlimb rigidity.
Chronic: 1000 ppm, at 15th mo. episodic hindlimb ataxia, later convulsions, no lesions reported at autopsy.

ANIMALS: Dogs, purebred beagle, 2 M and 2 F, age 6 mo.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0, 100, 400, 1000 ppm in diet for 2 yr (chronic toxicity); Subacute studies 0-3000 ppm.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Zero treatment

DURATION OF EXPERIMENT: 2 yr

EXAM. TYPE: Behavior, biochemistry (clinical), autopsy

10

COMPOUND: Acetamide, 2-fluoro-N-methyl-N-1-napthyl

005903139

REFERENCE: Hashimoto, Y., Noguchi, T., Mori, T. and Kitagawa, H.
Tox. Appl. Pharm. 13:174-188, 1968.

OBSERVED NEUROTOXIC EFFECTS: Toxic or lethal doses produced EEG's with no evidence of convusive pattern, but a flat wave pattern before death indicated severe brain impairment. Toxicity, judged small, was attributed to the metabolite, monofluoroacetic acid.

ANIMALS: Rats, albino, M, 150 g
10 Mice, M, 20 g
10 Guinea-pigs, albino, M, 350 g
In vitro
Rabbits
Cats
Dogs
Monkeys

PREPARATION AND DOSE or HISTORY OF PATIENT: Many schedules and dosages, acute and chronic; some animals prepared surgically.

ROUTE AND SITE: Various

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Many: EEG relevant here.

COMPOUND: Acetanilide, 2'-(2-bromo-3-thienyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Acetanilide, 4'-(4-(3-dimethyl amino)propyl)-1-piperazinyl)-

REFERENCE: Benitz, K.F. and Kramer, A.W.
Fd. Cosmet. Toxicol. 6: 125-133, 1968.

OBSERVED NEUROTOXIC EFFECTS: Hydrocephalus, oedema, hyperaemia and lesions of the brain. Vacuolization of the choroid plexus.

ANIMALS: Rats (CFN and Sherman), Mongolian Gerbils, Swiss Albino Mice, African Green Monkeys and Miniature Pigs (Pitman-Moore strain)

PREPARATION AND DOSE or HISTORY OF PATIENT: 60-488 mg/kg/d

ROUTE AND SITE: Oral, gavage

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial Sacr. 2 d to 50 wk

EXAM. TYPE: Histology

11^

COMPOUND: Acetanilide, 2'-(3-thienyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalapsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

12

COMPOUND: Acethydrazide

001068571

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2.1 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Acetic acid, bis(p-chlorophenyl)- (DDA, a metabolite of DDT)

REFERENCE: Bleiberg, M.J., Cefaratti, M., Klinman, N. and Kornblith, P.
Tox. Appl. Pharm. 4:292-312, 1962.

OBSERVED NEUROTOXIC EFFECTS: Blocked patellar reflex at doses over 2 mg/rabbit; in vitro block on choline acetylase, probably at the acetate activating step, in brain, and blocked in vitro peristalsis of gut preparations. Interpreted in terms of mode of action of toxicity of DDT.

ANIMALS: (1) Rabbits, white, 2.5-3.5 kg, surgically prepared.
(2) Rabbit small intestine in vitro.
(3) Guinea-pig ileum in vitro.
(4) Rabbit brains, powdered and acetone-dried.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Sodium salt of DDA used.
(1) In vivo single or successive doses 0.4-2.3 mg/rabbit.
(2&3) 10^{-4} to 10^{-3} M in medium, various schedules and combinations.
(4) AChE inhibition by 10 mcgM DDA in vitro.

ROUTE AND SITE: In vivo: intra-arterial, lumbar.

CONTROL INFORMATION: Yes

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Acetic acid, cyano-, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.8 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Acetic acid, (2,3-dichloro-4-(2-methylenebutryl) phenoxy)-

000058548

REFERENCE: Schneider, W.J. and Becker, E.L.
Arch. Inter. Med. 117:715-717, 1966.

OBSERVED NEUROTOXIC EFFECTS: Acute deafness.

ANIMALS: 5 Humans: 4 F, 1 M, age 20-76

PREPARATION AND DOSE
or HISTORY OF PATIENT: 150-700 mg.

ROUTE AND SITE: I.V. and oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, behavior, urinalysis

13A

14

COMPOUND: Acetic acid, 2,4-dichlorophenoxy-

REFERENCE: Desi, I. and Sos,J.
Acta Med. Acad. Sci. Hung. 18: 429-433, 1962.

OBSERVED NEUROTOXIC EFFECTS: Acute studies: reversible EEG inhibition. Chronic: gradual slowing of EEG and shortening of desynchronization times; disordered conditioned reflexes

ANIMALS: 24 rats, white, M, 240-250 g
4 cats
2 dogs

PREPARATION AND DOSE
or HISTORY OF PATIENT: 200 mg/kg/d (rat I.P. LD_{50} reported as 640 mg/kg)

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Untreated

DURATION OF EXPERIMENT: Up to 6 d

EXAM. TYPE: Behavior, electrophysiology

COMPOUND: Acetic acid, 2,4-dichlorophenoxy-

REFERENCE: Desi, I., Sos, J. and Nikolits, I.
Acta Physiol. Acad. Sci. Hung. 22: 73-80, 1962.

OBSERVED NEUROTOXIC EFFECTS: EEG: Lower frequency and greater amplitude at 24 hr; after 5 d, big, slow, toxic waves predominated. Little or no desynchronization response to reticular formation stimuli. The authors concluded that DCPA acted first on the cortex; the thyroid and cardiac disturbances being attributed to secondary subcortical lesions.

ANIMALS: 15 cats, 2.5-3.5 kg, 11 treated, all surgically prepared

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg/d 11 d

ROUTE AND SITE: ns

CONTROL INFORMATION: 4 cats

DURATION OF EXPERIMENT: 15 d

EXAM. TYPE: EEG

COMPOUND: Acetic acid, (2,4-dichlorophenoxy)-

000094757

REFERENCE: Goldstein, N.P., Jones, P.H. and Brown, J.R.
J. Am. Med. Assn. 171:1306-1309, 1959.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy. Delayed and prolonged polyneuritis, especially of lower limbs, slow nerve conduction, incomplete recovery.

ANIMALS: 3 Humans

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure during horticulture.

ROUTE AND SITE: Skin absorption

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 3 yr.

EXAM., TYPE: Clinical, electophysiology

COMPOUND: Acetic acid, (2,4-dichlorophenoxy)-, compound with dimethylamine (1:1)

002008391

REFERENCE: Berkley, H.C. and Magee, K.R.
Arch. Int. Med. 111:351-352, 1963.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, mainly sensory, gradual improvement after "several weeks".

ANIMALS: 1 Human, M, age 39

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure to agricultural spray

ROUTE AND SITE: Skin contact, probable inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Follow-up for 9 mo.

EXAM. TYPE: Physical; clinical laboratory; electromyography

16

COMPOUND: Acetic acid, (ethylene-dinitrilo) tetra-

000060004

REFERENCE: Swenerton, H. and Hurley, L.S.
Science 173:62-63, 1971.

OBSERVED NEUROTOXIC EFFECTS: Hydrocephalus, anencephalus, hydranencephalus, exencephalus, prevented by 1000 ppm of zinc in diet but not by 100 ppm. Author suggests the congenital anomalies caused, may be due to zinc deficiency.

ANIMALS: Rats, S-D, F, 210 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT:
(1) 2% or 3% in diet throughout.
(2) 3% in diet from d 6 to 21, or d 6-14 of pregnancy, followed by control diet until term.
(3) 3% in diet, plus 1000 ppm of zinc from d 6-21.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Rats fed control diet, without compound.

DURATION OF EXPERIMENT: Pregnancy

EXAM. TYPE: Teratology

COMPOUND: Acetic acid, fluoro-, sodium salt

000062748

REFERENCE: Corsi, A. and Granata, A.L.
Biochem. Pharmacol. 16:1083-1089, 1967.

OBSERVED NEUROTOXIC EFFECTS: No effect on respiration of brain mitochondria with any substrate. No effect on oxidation of glucose. Citrate found higher in brain homogenates from treated rats, but this could not be reproduced in vitro.

ANIMALS: Rats, Wistar

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20 mg/kg one dose, rats killed after 1 hr, brain mitochondria incubated in vitro with various substrates, slices and homogenates of brain cortex incubated with/without glucose.

ROUTE AND SITE: I.P., incubation In vitro.

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Acetic acid, iminodi

000142734

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, ô-amino-ß-hydroxybutyric, glycine, α-alanine, ô-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, iontophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

17

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Brown, S., Dragann, N. and Vogel, W.H.
Arch. Env. Hlth. 22:370-372, 1971.

OBSERVED NEUROTOXIC EFFECTS: No significant effects on learning or memory of rats as tested in water-filled T-maze.

ANIMALS: Rats, S-D, M, aged 8 d to 5 wk.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg/d, 3-4 in most cases.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Rats sodium acetate treated.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

18

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Carson, T.L., Van Gelder, G.A. Karas, G.G. and Buck, W.B. Env. Hlth. Persp. 7:233-237, 1974.

OBSERVED NEUROTOXIC EFFECTS: Poor performance of auditory discrimination task by adults, no change in reinforcement behavioral task. Lambs, no change in closed-field maze task, slow learning of nonspatial two-choice visual discrimination tasks at 10-15 mo. of age after prenatal exposure.

ANIMALS: Sheeps, 3 grps of 5 adults and 5 grps of 4 lambs.

PREPARATION AND DOSE or HISTORY OF PATIENT: Adults: 100 mg/kg/d for 9 wk, 120 and 230 mg/sheep/d for 27 wk.
Lambs: Exposed prenatally, 16 or 34 mcl/100 ml of blood, postnatal 2-16 mg/kg/d in diet.

ROUTE AND SITE: Oral, transplacental

CONTROL INFORMATION: Untreated controls

DURATION OF EXPERIMENT: Up to 15 mo.

EXAM. TYPE: Behavior

COMPOUND: Acetic acid, lead (2+) salt
000301042

REFERENCE: Golter, M. and Michaelson, I.A. Science 187:359-360, 1975.

OBSERVED NEUROTOXIC EFFECTS: More active than controls; more norepinephrine, no change of dopamine in brains (opposite findings to previous report, see under Lead carbonate, Sauerhoff and Michaelson.

ANIMALS: Rats, S-D, F, pregnant 16 d

PREPARATION AND DOSE or HISTORY OF PATIENT: (B) Neonates 1 mg of Pb in 0.1 ml for 15 d, then 40 ppm Pb in diet.
(C) Dams 5% Pb-acetate in diet till neonates 16 d old, then 40 ppm Pb in diet; neonates 40 ppm in diet from d 16, weaning.

ROUTE AND SITE: Oral

CONTROL INFORMATION: (A) Dams untrtd; neonates 0.1 ml of 2% Na-acetate d 1-15, then weaned onto normal diet.

DURATION OF EXPERIMENT: Serial sacr to 81 d of age of neonates.

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Michaelson, I.A. and Sauerhoff, M.W.
Env. Hlth. Persp. 7:201-225, 1974.

OBSERVED NEUROTOXIC EFFECTS: 30% less food eaten by lactating dams, offspring had 85% more lead than controls in cerebellum and cerebral cortex with 10-20% less DNA in cerebellum at 3 wk of age, paraplegia and cerebellar damage after eating lead diet. After 25 ppm lead in diet encephalopathy less severe: hyperactivity, tremors, stereotype behavior, 15-20% decrease of dopamine but no change in 5-HT, GABA or NE, no "debilitating histopathology."

ANIMALS: Rats, Porton, newborn with dams.

PREPARATION AND DOSE or HISTORY OF PATIENT: 4.5 or 5% in diet fed to dams and, at weaning, to litters. Diet gave 2.73% Pb, and produced milk containing 25 ppm Pb. Some diets adjusted to contain 25 ppm Pb.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Diets without lead, pair-feeding controls

DURATION OF EXPERIMENT: 30 d

EXAM. TYPE: Behavior, biochemistry

191

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Michaelson, I.A. and Sauerhoff, M.W.
Toxicol. Appl. Pharm. 28:88-96, 1974.

OBSERVED NEUROTOXIC EFFECTS: Histological lesions in the cerebellum and paraplegia. Hyperactivity, aggressiveness and tremors.

ANIMALS: Rats, S-D pregnant and offspring.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5% in diet to mothers immediately after birth, when offspring were 16 d old, mother's diet was changed to 25 ppm lead to compare to that in maternal milk.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Control sucklings, no treatment to mothers

DURATION OF EXPERIMENT: Sucklings sacr at 25 d age.

EXAM. TYPE: Histology

20<

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Schlaepfer, W.W.
J. Neuropath. Exp. Neurol. 28(3): 401-418, 1969.

OBSERVED NEUROTOXIC EFFECTS: Segmental demyelination and remyelination in peripheral nervous system and spinal nerve roots. Wallerian degeneration present in distal peripheral nervous system and in posterior nerve roots.
PNS: 6/14 axonal or Wallerian degeneration and 9/14 segmental demyelination and remyelination.
Spinal cord: Wallerian and segmental change.

ANIMALS: 18 Rats, S-D, 200-250 gm.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1% soln., avg. 60 cc/rat/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 3 Rats untreated.

DURATION OF EXPERIMENT: Serial sacr 3-18 mo.

EXAM. TYPE: Ultrastructural, histochemistry

COMPOUND: Acetic acid, lead (2+) salt

000301042

REFERENCE: Silbergeld, E.K. and Goldberg, A.M.
Life Sci. 13:1275-1283, 1973.

OBSERVED NEUROTOXIC EFFECTS: Induced hyperactivity (not dose-related), peripheral ataxia and splayed gait. 10 mg/ml for 90 days produced convulsions and death.

ANIMALS: Mice, age 12 hr

PREPARATION AND DOSE or HISTORY OF PATIENT: 2, 5, or 10 mg/ml in drinking water

ROUTE AND SITE: Oral

CONTROL INFORMATION: Age and dose matched with sodium acetate

DURATION OF EXPERIMENT: 90 d

EXAM. TYPE: Behavior

COMPOUND: Acetic acid, mercaptophenyl-, ethyl ester, S-ester with O,O-dimethyl phosphorodithioate

002597037

REFERENCE: Sherman, H., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hr. Survivors were lethargic for 6-19 hrs. post treatment. (2) 50% cholinesterase inhibition by dose <50 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (56.6 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

21^

COMPOUND: Acetic acid, thallium (1) salt

000563688

REFERENCE: Spencer, P.S., Peterson, E.R., Madrid, R. and Raine, C.S.
J. Cell Biol. 58: 79-95, 1973.

OBSERVED NEUROTOXIC EFFECTS: Mitochondria in axons of peripheral nerve fibers were enlarged after 2 hours, then mitochondria swelled to become axonal vacuoles, which coalesced, and the outer membranes had affinity for thallium which is electron-dense. Swelling made myelin retract from nodes of Ranvier, but there was no degeneration, and conduction was not lost. There were similar changes, but less severe, in dorsal root ganglia and central fibers, but not in other cell types.

ANIMALS: In vitro cross-sections of fetal mouse spinal cord with dorsal root ganglia, 14 d in utero

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 mcg/ml = 2×10^{-5} M

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Cultures grown for 12 wk, exposed to thallium for up to 4 d

EXAM. TYPE: Histology

11

22

COMPOUND: Acetic acid, p-tolyl-, 3-alpha-tropanyl ester

REFERENCE: Friess, S.L. and Anderson, J.B.
Tox. Appl. Pharm. 22: 208-212, 1972.

OBSERVED NEUROTOXIC EFFECTS: With the above compound or its quaternary methiodide separately, there was reversibility of induced blockade on washing depending on the extent of N-substitution, quaternary methiodide being more reversible than the tertiary ester. But 1 mM of tropine-p-tolylacetate added to 5mM of its quaternary methiodide halved the reversibility of quaternary methiodide blockade. More than 1 mM of tropine-p-tolylacetate had no more effect.

ANIMALS: In vitro excitable nodes of Ranvier in single fibers of frog sciatic nerve.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5mM for separate incubations with tropine-p-tolylacetate and its quaternary methiodide; tropine-p-tolylacetate:the quaternary methiodide ratios in mixed incubations 1:5, 2:5, and 3:5 in mM.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Incubation, removal, washing, observing by electrophysiology

COMPOUND: Acetic acid, zinc salt
000557346

REFERENCE: Prakash, N.J., Fontana, J. and Henkin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: At concentrations over 0.1 mM, Zn^{++} completely inhibited (Na^{+} + K^{+}) ATPase. Inhibition involved blockage of norepinephrine and choline uptake.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Zn acetate added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

COMPOUND: Acetone

000067641

REFERENCE: Rose, D.S.
Ann. Occup. Hyg. 16:73-75, 1973.

OBSERVED NEUROTOXIC EFFECTS: Urine level at least 4.6-7.15 mg% after exposure, 0.39-1.29 mg% 7 d later. Dizziness, unconsciousness, with recovery.

ANIMALS: 7 Human cases of industrial exposure

PREPARATION AND DOSE or HISTORY OF PATIENT: 900-12,000 ppm 2 min - 4 hr (acute exposure).

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 7 d ttmt afterwards

EXAM. TYPE:Clinical, urinalysis

COMPOUND: Acetone, allophanylhydrazone

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2.5 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

24

COMPOUND: Acetone semicarbazone

000110203

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.78 mM/kgm

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Acetone, thiocarbohydrazone

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.27mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Acetone, thiocarbohydrazonodi-

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.55 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

25

COMPOUND: Acetone thiosemicarbazone

001752303

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.18 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

26>

COMPOUND: Acetophenone, 2-chloro

000532274

REFERENCE: Rutledge, C.O. and Dietrich, R.A.
Biochem. Pharmacol. 20:193-201, 1971.

OBSERVED NEUROTOXIC EFFECTS: Inhibited norepinephrine catabolism. Inhibited formation of phenolic acids and enhanced that of phenolic glycols. In vitro aldehyde dehydrogenase was inhibited (prevented with glutathione, reversed with sulfhydryl reagents).

ANIMALS: Rabbits, adult M, 2.0-2.5 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: In vivo pretreatment: 300 mg/kg in 100% EtOH (1.33 g/kg). In vitro incubation of brain cortex xlices (150 mg) with and without 2-chloroacetophenone.

ROUTE AND SITE: I.P.; addition to medium.

CONTROL INFORMATION: Pretreatment: ethanol only. In vitro: HCl.

DURATION OF EXPERIMENT: In vitro: 30-40 min.

EXAM. TYPE: Biochemical

COMPOUND: Acetophenone, thiocarbohydrazone

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1.2 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Acrylamide

000079061

REFERENCE: Auld, R.B. and Bedwell, S.F.
Can. Med. Assn. J. 96:652-654, 1967.

OBSERVED NEUROTOXIC EFFECTS: Contact dermatitis with polyneuropathy of extremities attributed to sympathetic overactivity. Complete recovery in 3 mo. "Believed" to have resulted from acrylamide, and claimed as the first human case-report.

ANIMALS: Human: 1 case-report, M aged 21 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Industrial exposure to 10% aqueous solution 35 hr/wk, signs after 2 wk, hospitalized after 3 mo.

ROUTE AND SITE: Skin contact, especially face and forearms

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Observations total 6.5 mo.

EXAM. TYPE: Clinical, hospital laboratory

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COMPOUND: Acrylamide

000079061

REFERENCE: Barnes, J.M.
Brit. J. Indust. Med. 27:147-149, 1970.

OBSERVED NEUROTOXIC EFFECTS: (1) Most rats died within a few days. The rest had signs of gross general weakness. (2) Within four weeks, signs of disability appeared; marked by eight weeks.

ANIMALS: Rats, Porton, albino

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Two doses, 100 mg/kg
(2) 400 ppm

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 10 wk

EXAM. TYPE: Behavior, physiology

COMPOUND: Acrylamide

000079061

REFERENCE: Edwards, P.M.
Br. J. Ind. Med. 32:31-38, 1975.

OBSERVED NEUROTOXIC EFFECTS:
(1) Rats: Ataxia, waddling gait, hindlimb weakness.
(2) Hens: Slight ataxia; degeneration of sciatic and peroneal nerve fibers and medullary and cervical spinocerebellar tracts.
(3,4) Frogs, goldfish: sublethel effects varying with dosage.

ANIMALS:
(1) Rats, Porton, M, 200 g
(2) Hens, Star Cross, adult, 3 leg
(3) Frogs, R. Temporaria, M
(4) Goldfish

PREPARATION AND DOSE or HISTORY OF PATIENT: Dose varied with species

ROUTE AND SITE: (1) Oral, I.P. (3) Dorsal sac injection or via exposure
(2) Oral (4) Through natural habitat

CONTROL INFORMATION: Vehicles only

DURATION OF EXPERIMENT: Up to 13 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Acrylamide

000079061

REFERENCE: Fullerton, P.M. and Barnes, J.M.
Br. J. Indust. Med. 23:210-221, 1966.

OBSERVED NEUROTOXIC EFFECTS: Ataxia and limb weaknesses at single or repeated doses of 25-100 mg/kg (gavage) or 100-400 ppm (diet). Severe cases 20% slower nerve conduction. Degeneration of myelin and axis cylinders in long fibers of peripheral nervous system. On stopping treatment, clinical recovery, normalized conduction, and some histological regeneration.

ANIMALS: Rats, Porton, M and F, various ages.

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 100 mg/kg, one dose, or two doses on successive days.
(2) 50 mg/kg/d, 12 doses in 15 d.
(3) 25 mg/kg/d, 5 d/wk.
(4) 10 mg/kg/d for 55 or 116 doses.
(5) 100 mg/kg twice/wk, once/wk, once/10 d, once/14 d.
(6) Diets with 0-400 ppm (greatest intake 30 mg/kg/d).

ROUTE AND SITE: Gavage or oral (diet).

CONTROL INFORMATION: Only in (6), diet alone.

DURATION OF EXPERIMENT: Up to 52 wk.

EXAM. TYPE: Behavior, electrophysiology, histology

COMPOUND: Acrylamide

000079061

REFERENCE: Fullerton, P.M.
J. Neurol. Neurosurg. Psychiat. 32:186-192, 1969.

OBSERVED NEUROTOXIC EFFECTS: Sural nerve biopsies from the lateral malleolus (ankle), showed degeneration and regeneration thought to have begun before onset of symptoms. Sensory nerve action potentials were weak or absent; motor conduction was slow.

ANIMALS: Human: 3 cases, M (already reported by Garland & Patterson 1967).

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) Exposure for 1 mo, symptoms then progressive for 2 mo.
(2) Exposure for 6 wk, then severely disabled after 6 wk.
(3) Exposure for 18 mo, then symptoms progressive for 2 mo and recovery incomplete 10 wk later.

ROUTE AND SITE: ns.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 2-1/2 yr

EXAM. TYPE: Electrophysiology, histology

29>

COMPOUND: Acrylamide

000079061

REFERENCE: Hashimoto, K. and Ando, K.
Biochem. Pharm 22:1057-1066, 1973.

OBSERVED NEUROTOXIC EFFECTS: Hindlimb weakness at 2 wk, paralysis at 4 wk, clinical recovery 5-6 wk after ttmt ended. Incorporation of labeled lysine and methionine into proteins of sciatic nerve and spinal cord altered by compound.

ANIMALS: Rats, SD, M, 8 wk old. Groups of 3, 5, or 15.

PREPARATION AND DOSE or HISTORY OF PATIENT: 500 ppm in "Oriental M" powder diet for 4 wk, followed by 4 wk control diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Groups fed powder diet only.

DURATION OF EXPERIMENT: Up to 6 wk after ttmt, sacr

EXAM. TYPE: Behavior; radioautography; biochemistry.

30

COMPOUND: Acrylamide

000079061

REFERENCE: Igisu, H., Goto, I., Kawamura, Y., Kato, M., Izumi, K. and Kuroiwa, Y.
J. Neurol. Neurosurg, Psychiat. 38:581-584, 1975.

OBSERVED NEUROTOXIC EFFECTS: Signs appeared 3 wk after act of contamination, subacute mental confusion and/or truncal ataxia; good recovery within 4 mo.

ANIMALS: Human: 1 family of 5 (F 65, M 42, F 40, M 13, F 10)

PREPARATION AND DOSE or HISTORY OF PATIENT: Well-water found to contain 400 ppm, from roadworks performed 1 mo. before sampling; exposure max 4 wk.

ROUTE AND SITE: Oral, skin contact

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 mo., plus follow-up 4 mo.

EXAM. TYPE: Clinical, electrophysiology

COMPOUND: Acrylamide

000079061

REFERENCE: Kaplan, M.L., Murphy, S.D. and Gilles, F.H.
Tox. Appl. Pharm. 24:564-579, 1973.

OBSERVED NEUROTOXIC EFFECTS: Cumulative total to produce neurologic deficit was 360 mg/kg in controls, to 600 mg/kg in Phenobarbital-premedicated. The latter and young rats had severe peripheral nerve damage; unpretreated adults did not. Rotarod appratus used to measure neurologic deficit.

ANIMALS: Rats, Holtzman, M, 200-300 g or 5 wk old.

PREPARATION AND DOSE or HISTORY OF PATIENT: Daily aq soln, various compounds given to modify the "neurologic deficit." Complex schedules. Some rats adrenalectomized.

ROUTE AND SITE: I.P., in vitro

CONTROL INFORMATION:

DURATION OF EXPERIMENT:

EXAM. TYPE: Behavior, histology, in-vitro.

COMPOUND: Acrylamide

000079061

REFERENCE: Kuperman, A.S.
J. Pharm. Exp. Ther. 123:180-192, 1958.

OBSERVED NEUROTOXIC EFFECTS: Lethal doses produced convulsions; sublethal doses produced ataxia and tremors like cerebellar asynergia. No other biological effects, no histological alterations. Primary site of non-convulsive action was subcortical, diffuse; author infers the mesencephalic tegmentum as the primary site of intoxication.

ANIMALS: Cats, intact and surgically prepared: spinal cord transection, decerebellation, decortication, or decerebration.

PREPARATION AND DOSE or HISTORY OF PATIENT: Nonconvulsive doses of 1-50 mg/kg/d. Convulsive single doses of 75-1000 mg/kg. Many schedules used, acrylamide 99.2% pure in water.

ROUTE AND SITE: I.V. or I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Different schedules.

EXAM. TYPE: Behavior, EEG, histology.

COMPOUND: Acrylamide

000079061

REFERENCE: Leswing, R.J. and Ribelin, W.E.
Arch. Env. Hlth. 18: 22-29, 1969

OBSERVED NEUROTOXIC EFFECTS: Paralysis, especially hindlimbs, at higher dosage in monkeys. Conduction in sciatic nerves 28% slower in cats, 22% in monkeys, 20% in ulnar nerve of monkeys, with longer latencies. Degeneration of myelin and axons in affected nerves. When treatment stopped, signs improved.

ANIMALS: (1) 11 cats, unselected young adults
(2) 4 Cebus albifrons monkeys

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Cats: 20 mg/kg/d
(2) Monkeys: 20 mg/kg/d for 8 wk, then 30 mg/kg/d

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, electrophysiology, histology

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COMPOUND: Acrylamide

000079061

REFERENCE: McCollister, D.D., Oyen, F. and Rowe, V.K.
Tox. Appl. Pharm. 6:172-181, 1964.

OBSERVED NEUROTOXIC EFFECTS: Weakness and ataxia, starting in hindlimbs. Recovery of survivors prolonged according to dose(s); "no nerve tissue pathology has been found in the affected animals, not even in those severely intoxicated to the point of death."

ANIMALS: Monkeys, F (no other details)
Rats, Dow-Wistar, M and F, about 60 d old
Guinea-pigs, M
Rabbits, M and F
Cats (no details)

PREPARATION AND DOSE or HISTORY OF PATIENT: Various schedules

ROUTE AND SITE: Gavage (one dose); skin contact; eye contact; I.P.; I.V.; diet (oral)

CONTROL INFORMATION: Zero dosage

DURATION OF EXPERIMENT: Up to 1 yr (diet, cats and monkeys)

EXAM. TYPE: Clinical, pathology

COMPOUND: Acrylamide

000079061

REFERENCE: Morgan-Hughes, J.A., Sinclair, S. and Durston, J.H.J.
Brain 97:235-250, 1974.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, flacid weakness of the hindlimbs, retarded nerve growth. Axonal degeneration Crush injury healed in 8 wk in controls, healing delayed or inhibited in those treated. Less regeneration and when regeneration occured it was less than usual.

ANIMALS: 20 Rats, Wistar, 300-440 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 200 ppm (12 rats) or 300 ppm (2 rats) in diet. Right sciatic crush injury 7-22 wk after start of experiment.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 14 matched rats, untreated.

DURATION OF EXPERIMENT: Up to 30 wk after sciatic crush

EXAM. TYPE: Electrophysiology, histology, clinical

COMPOUND: Acrylamide

000079061

REFERENCE: Prineas, J.
J. Neuropath. Exp. Neurol 28(4):598-621, 1969.

OBSERVED NEUROTOXIC EFFECTS: Left tibial nerve and right anterior horn cells of cord showed "dying-back changes" of axons. Subcellular changes differed from those due to TOCP. Behavior "was very similar to that seen in TOCP intoxication," progressive weakness of limbs starting with hind limbs.

ANIMALS: 6 Cats, M and F, 2.5-4.0 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 5 cats: 10 mg/kg/d in 2 ml water.
(2) 1 cat: 150 mg/kg in 2 doses, 21 hr apart.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 4 Cats from another study.

DURATION OF EXPERIMENT: Serial sacr up to 49 d

EXAM. TYPE: Behavior, histology

COMPOUND: Acrylamide

000079061

REFERENCE: Schaumberg, H.H., Wisniewski, H.M., and Spencer, P.S.
J. Neuropathol. Exp. Neurol 33:260-284, 1974.

OBSERVED NEUROTOXIC EFFECTS: Unsteady gait, head tremor and distal muscle weakness. Loss of peripheral myelinated fibers, unmyelinated were preserved. Degeneration of Pacinian corpuscles, muscle spindles, and some neuromuscular junctions, consistent with dying back.

ANIMALS: 12 Cats, 3 aged 1 yr or more, 9 aged less.

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 10 mg/kg/d.
(2) 10 mg/kg alternating with 20-40 mg/kg.
(3) 3 mg/kg/d in drinking water.

ROUTE AND SITE: (1) I.P. (2) I.P. (3) Oral

CONTROL INFORMATION: 6 control cats.

DURATION OF EXPERIMENT: 7-294 d, irregular schedules.

EXAM. TYPE: Behavior, histology (biopsy and autopsy)

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COMPOUND: Acrylamide

000079061

REFERENCE: Suzuki, K. and Pfaff, L.D.
Acta Neuropath 24:197-213, 1973.

OBSERVED NEUROTOXIC EFFECTS: Weakness of limb muscles, recovered after 1-2 mo., some adults had hindlimb paralyzed. Axonal degeneration, demyelination in sciatic nerve, regeneration observed.

ANIMALS: Rats, Osborn-Mendel, 30 suckling-5 to 8 g, 28 adults 150-300 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50 mg/kg in saline, 3/wk to 18 doses, 2 adults had 26 doses.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 12 rats saline only

DURATION OF EXPERIMENT: Up to about 4 mo.

EXAM. TYPE: Histology of sciatic nerve

COMPOUND: Acrylamide, N,N-diethyl-

REFERENCE: Edwards, P.M.
Br. J. Ind. Med. 32:31-38, 1975.

OBSERVED NEUROTOXIC EFFECTS:
(1) Rats: Ataxia, waddling gait, hindlimb weakness.
(2) Hens: Slight ataxia; degeneration of sciatic and peroneal nerve fibers and medullary and cervical spinocerebellar tracts.
(3,4) Frogs, goldfish: sublethel effects varying with dosage.

ANIMALS:
(1) Rats, Porton, M, 200 g
(2) Hens, Star Cross, adult, 3 leg
(3) Frogs, R. Temporaria, M
(4) Goldfish

PREPARATION AND DOSE
or HISTORY OF PATIENT: Dose varied with species

ROUTE AND SITE: (1) Oral, I.P.
(2) Oral
(3) Dorsal sac injection or via exposure
(4) Through natural habitat

CONTROL INFORMATION: Vehicles only

DURATION OF EXPERIMENT: Up to 13 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Acrylamide, N-hydroxymethyl-

REFERENCE: Barnes, J.M.
Brit. J. Industr. Med. 27:147-149, 1970.

OBSERVED NEUROTOXIC EFFECTS: "Fine tremors and were generally affected." No gross signs of weakness.

ANIMALS: 6 young Adult rats, Porton Strain, M

PREPARATION AND DOSE
or HISTORY OF PATIENT: 7 doses of 100 mg/kg in 12 d.
2 doses of 200 mg/kg on day 23 and 24.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 37 d.

EXAM. TYPE: Behavior, physiology

COMPOUND: Acrylamide, N-hydroxymethyl-

REFERENCE: Edwards, P.M.
Br. J. Ind. Med. 32:31-38, 1975.

OBSERVED NEUROTOXIC EFFECTS:
(1) Rats: Ataxia, waddling gait, hindlimb weakness.
(2) Hens: Slight ataxia; degeneration of sciatic and peroneal nerve fibers and medullary and cervical spinocerebellar tracts.
(3,4) Frogs, goldfish: sublethal effects varying with dosage.

ANIMALS:
(1) Rats, Porton, M, 200 g
(2) Hens, Star Cross, adult, 3 leg
(3) Frogs, R. Temporaria, M
(4) Goldfish

PREPARATION AND DOSE
or HISTORY OF PATIENT: Dose varied with species

ROUTE AND SITE: (1) Oral, I.P.
(2) Oral
(3) Dorsal sac injection or via exposure
(4) Through natural habitat

CONTROL INFORMATION: Vehicles only

DURATION OF EXPERIMENT: Up to 13 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Acrylamide, N-methyl

REFERENCE: Barnes, J.M.
Brit. J. Industr. Med. 27:147-149, 1970.

OBSERVED NEUROTOXIC EFFECTS: 2 of the 3 had definite weakness like mild acrylamide poisoning. One rat died after second series of doses.

ANIMALS: (1) 6 Rats, Porton, Albino, M
(2) 4 Rats, Porton, Albino, M
(3) 3 Rats, Porton, Albino, M

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 400 ppm for 10 wks followed by 3 wks at 800 ppm.
(2) 7 doses of 100 mg/kg for 2 wks.
(3) 10 doses of 50 mg/kg, then 11 doses of 100 mg/kg for 3 wks.

ROUTE AND SITE: (1) diet (2) — (3) oral dose

CONTROL INFORMATION: 2 animals, not described.

DURATION OF EXPERIMENT: Approximately 18 wks

EXAM. TYPE: Behavior, physiology

COMPOUND: Acrylamide, N-methyl

REFERENCE: Edwards, P.M.
Br. J. Ind. Med. 32:31-38, 1975.

OBSERVED NEUROTOXIC EFFECTS: (1) Rats: Ataxia, waddling gait, hindlimb weakness
(2) Hens: Slight ataxia; degeneration of sciatic and peroneal nerve fibers and medullary and cervical spinocerebellar tracts.
(3,4) Frogs, goldfish: sublethel effects varying with dosage.

ANIMALS: (1) Rats, Porton, M, 200 g
(2) Hens, Star Cross, adult, 3 leg
(3) Frogs, R. Temporaria, M
(4) Goldfish

PREPARATION AND DOSE or HISTORY OF PATIENT: Dose varied with species

ROUTE AND SITE: (1) Oral, I.P. (3) Dorsal sac injection or via exposure
(2) Oral (4) Through natural habitat

CONTROL INFORMATION: Vehicles only

DURATION OF EXPERIMENT: Up to 13 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Acrylamide monomer

REFERENCE: Garland, T.O. and Patterson, M.W.H.
Br. Med. J. iv:134-138, 1967.

OBSERVED NEUROTOXIC EFFECTS: Limb numbness and paresthesias, weakness, sweating and peeling, ataxia, lethargy, tremors, slurred speech, wt loss, bladder dysfunction; authors infer peripheral neuropathy and midbrain disturbance. Recovery 2-12 mo., not always complete.

ANIMALS: Human: 6 cases, M, aged 19-59

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to process of polymerization in manufacturing of flocculators.

ROUTE AND SITE: Skin of hands and inhalation of dust.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Exposure of 4 wk to over 1 yr.

EXAM. TYPE: Clinical

COMPOUND: Acrylic acid, 2-cyano-, methyl ester

000137053

REFERENCE: Dutton, J. and Yates, P.O
J. Neurosurg. 24: 876-882, 1966.

OBSERVED NEUROTOXIC EFFECTS: The dura matter in the brain of 13 cats was incised and then closed with a fascial graft and coated with the compound. 9 reacted and later healed, with no underlying damage and no damage to controls. Vertical incisions in the brain of 5 cats showed the death of neurons and glial response. Saphenous nerves were coated (30 cats) with 8 showing perineural inflammation and some damage to neurolemma and axons. All specimens showed inflammatory or granulomatous response, and fibrin proliferated between glue and tissues.

ANIMALS: Cats, M & F, 2-2.5 kg, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Experimental brain incisions (unilateral) were coated with compound.

ROUTE AND SITE: Topical

CONTROL INFORMATION: Saline contralaterally

DURATION OF EXPERIMENT: 3 d to 8 wk

EXAM. TYPE: Autopsy, histology

38

COMPOUND: Acrylic acid, 2-cyano-, methyl ester

000137053

REFERENCE: Kline, D.G. and Hayes, G.J.
J. Neurosurg. 20: 647-654, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound caused inflammation in all cases, tubular and axonal damage in most, and necrosis of neurons (no damage in any controls). In monkeys, inflammation, necrosis, demyelination and loss of axons were observed. The authors commented that the compound was not well tolerated by nerve tissues.

ANIMALS: Dogs, mongrel, M & F, 30-45 lbs, 2 grps of 10, surgically prepared.
Monkeys, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: Dogs: Part-isolated peroneal nerves of both hindlegs, one coated with compound, the other with saline. Bilateral trephination, 5 drops of compound applied to cortex, same of saline to other side.
Monkeys: Optic-chiasm implants.

ROUTE AND SITE: Topical

CONTROL INFORMATION: Saline

DURATION OF EXPERIMENT: Serial 2-12 wk

EXAM. TYPE: Autopsy, histology

COMPOUND: Actinomycin D

000050760

REFERENCE: Torvik, A., and Heding, A.
Acta Neuropath. 9: 146-157, 1967.

OBSERVED NEUROTOXIC EFFECTS: Animals treated i.p. had no histologic brain changes. After intracerebral treatment changes in all neurons from the anterior part of the brain to sacral segments of spinal cord. Control animals: changes at injection site only. Neurons nucleoli disintegrated rapidly. Retrograde reactions due to sectioning are blocked by Actinomycin D when injection given at time of operation.

ANIMALS: 75 mice, albino, 60-75 d old, 20-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 3 mice: 1.5 mcg in 0.07 ml water, every 3hr for 48hr, VIIth (facial) nerve sectioned.
(2) 14 mice: 1.5 mcg in 0.03 ml water or 0.9% saline, every 3-4 hr for 2-48 hr.
(3) 14 mice: as above, first inj given at time of operation to facial nerve.
(4) 12 mice: as above, except doses begun 48hr after operat

ROUTE AND SITE: I.P. and Intracerebral.

CONTROL INFORMATION: Control groups: vehicle alone, operation only, vehicle and operation.

DURATION OF EXPERIMENT: Serial sacr to 4d

EXAM. TYPE: Histology

COMPOUND: Adenosine, 3'-(alpha-amino-p-methoxy hydrocennamamido)-3'-deoxy-N,N-dimethyl (Puromycin)

000053792

REFERENCE: Moss, E.E., Moss, D.R. and Fahrney, D.
Pharm. Biochem. Behav. 2: 271-275, 1974.

OBSERVED NEUROTOXIC EFFECTS: Puromycin gave 50% inhibition of the cholinesterase at 0.5mM with 50mM substrate. The authors inferred that puromycin binds at two enzyme sites, one of which is allosteric.

ANIMALS: In vitro rat brain cholinesterase preparation.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various

ROUTE AND SITE: In vitro

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry

36A

COMPOUND: Adenosine, 3'-(alpha-amino-p-methoxy hydrocennamamido)-3'-deoxy-N,N-dimethyl (Puromycin)

000053792

REFERENCE: Zech, R. and Domagk, G.F.
Brain Res. 86:339-342, 1975.

OBSERVED NEUROTOXIC EFFECTS: Puromycin inhibited the activity of the enzyme, noncompetitively and reversibly.

ANIMALS: In vitro human brain acetylcholinesterase

PREPARATION AND DOSE
or HISTORY OF PATIENT: Chemical enzyme inhibition system

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

40

COMPOUND: Alanine, 3-(3,4-dihydroxyphenyl)-, L-

000059927

REFERENCE: Marotzky, R., Griffith, D., Stahl, S., Bondareff, W. and Zeller, E.A. Exp. Neurol. 38:218-230, 1973.

OBSERVED NEUROTOXIC EFFECTS: Increased spontaneous motor activity and pain responses with decrease of norepinephrine, interpreted with respect to psychiatric side-effects of parkinsonism therapy.

ANIMALS: Rats, S-D, M, 1.5-2 yr old, 3-4 per group

PREPARATION AND DOSE or HISTORY OF PATIENT: 12.5-62.5 mg/kg, or 250-1000 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle only; untrtd.

DURATION OF EXPERIMENT: 1-20 hr.

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Alanine, 3-mercapto-, hydrogen sulfate (ester)

REFERENCE: Olney, J.W., Misra, C.H., De Gubareff, T. J. Neuropath. Exp. Neurol 34(2):167-177, 1975.

OBSERVED NEUROTOXIC EFFECTS: Induction of glutamate type of neuropathology in rat central nervous system.
(1) Lesions in retina and arcuate nucleus of hypothalamus.
(2) Neuron-necrotizing lesion in brain, acute neuronal degeneration.

ANIMALS: (1) 18 Rats, Wistar albino, 5 days old
(2) Rats, Holtzman, adult

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1 injection at one of 3 doses (0.04, 0.4 and 4.0 m moles/kg) aqueous, pH 7.0 $\pm$ 0.1.
(2) 2 mcl of 77 mM soln, total dose 0.15 mc moles.

ROUTE AND SITE: (1) S.C. (2) Intracerebral

CONTROL INFORMATION: (1) 6 litter-mate injected subcut. with NaCl, 4 m moles/kg.
(2) 3 rats: 2 mcl inj 154 mM NaCl, 3 rats: cannulated no other treatment.

DURATION OF EXPERIMENT: Sacr after 3 hrs following injections.

EXAM. TYPE: Histology.

COMPOUND: Alanine, N-methyl-3-sulfo-, L- (N-methyl-L-cysteic acid)

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Alanine, phenyl-, L-

REFERENCE: Adelman, L.S., Mann, J.D., Caley, D.W. and Bass, N.H.
J. Neuropath. Exp. Neurol. 33(2):380-393, 1974.

OBSERVED NEUROTOXIC EFFECTS: Neuropathic lesions in the cerebellum. Axonal swelling.

ANIMALS: 12 Rats, CD^{R}, 14-16 days gestation
108 Weanling rats.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.9 mg/kg/d.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 18, dose and age matched.

DURATION OF EXPERIMENT: Serial sacr. 8, 13, 15, 20, 30, and 50

EXAM. TYPE: Microscopy, neuropathology

11
425

COMPOUND: Alanine, phenyl-, L-

REFERENCE: Shah, S.N., Peterson, N.A. and McKean, C.M.
J. Neurochem. 19:479-485, 1972.

OBSERVED NEUROTOXIC EFFECTS: Reduced cholesterol, glycolipids, and myelin in brains; DNA and protein unchanged, myelin composition unchanged. Authors inferred cholesterol reduction as the mechanism.

ANIMALS: Rats, S-D, aged 5 d

PREPARATION AND DOSE
or HISTORY OF PATIENT: 3 mg/g/d in 3 doses for 5, 10, 15 d.

ROUTE AND SITE: I.M.

CONTROL INFORMATION: Controls: saline only

DURATION OF EXPERIMENT: Serial sacr to 30 d

EXAM. TYPE: Biochemistry

COMPOUND: Alanine, 3-sulfino-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, sulfino-alanines, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Alanine, 3-sulfino-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

43

COMPOUND: Alanine, 3-sulfo-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

44

COMPOUND: Alanine, 3-sulfo-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Alanine, 3-sulfo-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Alanine, 3-sulfo-, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

45>

COMPOUND: Alanine, 3-(2-thienyl)-

REFERENCE: Capobianco, J.O. and Beck, S.L.
Teratology 4:295-302, 1971.

OBSERVED NEUROTOXIC EFFECTS: Prenatal treatment during "period of accelerated neural growth and differentiation" resulted in decreased brain weight and increased body wt compared to controls. Treated offspring had more sound-induced seizures than untreated controls, but not more than solvent-treated. Sound-stressed mice had lower brain catecholamine levels.

ANIMALS: Mice, 12th-13th generations of 4-way outcross of C3H/HeH, CBA/Gr, A/Gr, and C57BL/Gr strains, pregnant females. Total: 480 animals.

PREPARATION AND DOSE or HISTORY OF PATIENT: 40, 60 or 70 mg in 1 ml saline, 0.1 N HCl and 0.1 N NaOH (18:1:1) per d, on d 10-12 of gestation.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Groups of solvent ttd and unttd animals.

DURATION OF EXPERIMENT: Sacr 23 d postnatal

EXAM. TYPE: Sound-stress, and biochemistry

46

COMPOUND: Alanine. 2.4,5-trihydroxyphenyl-

REFERENCE: Richardson, J.S., Cowan,N., Hartman, R. and Jacobowitz, D.M.
Res. Comm. Chem. Path. Pharm. 8(1):29-44, 1974.

OBSERVED NEUROTOXIC EFFECTS: Lowered norepinephrine 25-50%; in combination with 5,6-dihydroxytryptamine (I) lowered norepinephrine and serotonin; no effect on dopamine. Alone or in combination with I, lowered food and water intakes. Alone, but not in combination with I, lowered spontaneous locomotion. Increased emotionality scores; I attenuated the increase. Other complex effects reported, and the causes speculated to be selective destruction of noradrenergic and/or serotonergic nerve terminals.

ANIMALS: Rats, S-D, M, 180-200 g, 5-12/group

PREPARATION AND DOSE
or HISTORY OF PATIENT: 90 mcg/rat

ROUTE AND SITE: Intraventricular

CONTROL INFORMATION: Vehicle

DURATION OF EXPERIMENT: 14 d

EXAM. TYPE: Behavior

COMPOUND: Alanine, 2,4,5-trihydroxyphenyl-

REFERENCE: Sachs, C. and Jonsson, G.
J. Neurochem. 19:1561-1575, 1972.

OBSERVED NEUROTOXIC EFFECTS: Doses (1) lethal, (2) MTD. Degeneration of central and peripheral norepinephrine neurons, mediated by decarboxylation of 6-OH-DOPA to 6-OH-Da. Neither 5-HT neurons nor dopamine neurons were affected.

ANIMALS: Mice, N.M.R.I., M, 25-30 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 250 or 400 mg/kg, one dose.
(2) 100 mg/kg, 1-6 doses at intervals.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls untreated.

DURATION OF EXPERIMENT: Up to 42 d

EXAM. TYPE: Biochemistry, fluorescence histochemistry

COMPOUND: Alanine, 2,4,5-trihydroxyphenyl-, hydrobromide

REFERENCE: Bonagura, V., Cassebaum, L., Dangman, K., Freund, J., Cabbat, F., Dembiec, D., Heikkila, R. and Cohrn, G.
Res. Comm. Chem. Path. Pharm. 4: 163-171, 1972.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused diminished uptake of norepinephrine, resulting from destruction of adrenergic nerve terminals. Accumulation of the compound at site needed for these effects. Desipramine, 25 mg/kg, protected under conditions of this experiment.

ANIMALS: Mice, Swiss-Webster, M, 25g

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline

DURATION OF EXPERIMENT: 72 hr

EXAM. TYPE: Biochemistry of heart slices

427

COMPOUND: Alkyl mercury

REFERENCE: Charlton, K.M.
Can. J. Comp. Med. 38(1):75-81, 1974.

OBSERVED NEUROTOXIC EFFECTS: Weakness of gait, blindness in affected pigs, aimless walking, reflexes minimally altered, death. Peripheral nervous system: Wallerian degeneration of sensory fibers, neuronal degeneral of dorsal root ganglia. Central nervous system: degeneration of neurons and glia.

ANIMALS: 20 Pigs, Yorkshire, 7 M and 13 F, aged approx. 10 wk.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.24-5.76 mg/kg/d of mercury for 11-199 d.

ROUTE AND SITE: ns.

CONTROL INFORMATION: 4 of above kept as controls, untreated

DURATION OF EXPERIMENT: Killed on d 13-205.

EXAM. TYPE: Behavior, histology

COMPOUND: Allophanic acid, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2.5 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Aloes

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115:199-205, 1975.

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus of colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m.

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

COMPOUND: Aluminum hydroxide

REFERENCE: Fleischhauer, K. and Schmalbach, K.
Acta Neuropath. 11:311-329, 1968.

OBSERVED NEUROTOXIC EFFECTS: No effect in nonmyelinated white-matter of juveniles; severe demyelination and gliosis of white-matter in adults, with added effects on grey-matter.

ANIMALS: 10 cats, various ages, in 3 grps.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.03-0.12 ml, one dose.

ROUTE AND SITE: Intracerebral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr: 7 d, 40 d, 3 mo.

EXAM. TYPE: Histology.

46A

COMPOUND: Ammonium, (O-bromobenzyl)ethyldimethyl-, p-toluenesulfonate
000061756

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} >40 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

50A

COMPOUND: Ammonium, (3-carboxypropyl) trimethyl-, carboxylate

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Ammonium, dibutyl(2-hydroxyethyl)methyl-

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other amino-ethanols and choline analogs, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-amino-ethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values. When given i.p., compound reduced brain cholinesterase.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ammonium, diethyl(2-hydroxyethyl)methyl-

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols and choline analogs, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-amino-ethanol molecule. In the in vivo tests the oral LD_{50} were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE
or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

51^

COMPOUND: Ammonium, (2-hydroxyethyl)triethyl-

REFERENCE: Bhatnagar, S.P., Lam, A. and McColl, J.D.
Biochem. Pharm. 14: 421-434, 1965.

OBSERVED NEUROTOXIC EFFECTS: Muscular weakness, respiratory paralysis, failure of transmission at cholinergic synapses; inhibition of acetylcholine synthesis.

ANIMALS: Mice, CFW, F, 15-20 g and mouse brain tissues in vitro
Cats, M & F, 2-3 kg, surgically prepared
In vitro reaction mixtures

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various doses

ROUTE AND SITE: Various routes

CONTROL INFORMATION: Various controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Chemistry, electrophysiology

52A

COMPOUND: Ammonium, (2-hydroxyethyl) triethyl-, p-toluenesulfonate, 3,4,5-trimethoxybenzoate

REFERENCE: Bhatnagar, S.P., Lam, A. and McColl, J.D.
Biochem. Pharm. 14: 421-434, 1965

OBSERVED NEUROTOXIC EFFECTS: Muscular weakness, respiratory paralysis, failure of transmission at cholinergic synapses; inhibition of acetylcholine synthesis.

ANIMALS: Mice, CFW, F, 15-20 g and mouse brain tissues in vitro
Cats, M & F, 2-3 kg, surgically prepared
In vitro reaction mixtures

PREPARATION AND DOSE or HISTORY OF PATIENT: Various doses

ROUTE AND SITE: Various routes

CONTROL INFORMATION: Various controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Chemistry, electrophysiology

COMPOUND: Ammonium, (m-hydroxyphenyl)trimethyl-, bromide, dimethylcarbamate
000114807

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: Produced variable results, ranging from reversal to enhancement of neuromuscular blockade.

ANIMALS: 4 Rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: 25-100 mcg/kg administered at peak of the neuromuscular blockade from lincomycin (50 mg/kg).

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

COMPOUND: Ammonium ion (+1)

REFERENCE: Lux, H.D., Loracher, C. and Neher, E.
Exp. Brain Res. 11: 431-447, 1970.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused reversible reductions of IPSP-equilibrium potential which were more sensitive to extracellular and systemic ammonium than to intracellular ammonium. The authors suggest that slow release from inside the cells explains the long duration effects after intracellular applications. The effective extracellular doses corresponded to intracerebral concentrations of compound reported for preconvulsive states of epilepsies induced metabolically.

ANIMALS: 45 Cats, adult, 1.5-2.5 kg, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Compound applied by iontophoresis to exposed neurons, both intra- and extra-cellularly

ROUTE AND SITE: See above

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Various to 120 min

EXAM. TYPE: Electrophysiology

53<

COMPOUND: Androst-5-en-3-beta-ol, 17-beta-((3-(dimethylamino)propyl)methylamino)-

001249849

REFERENCE: Suzuki, K., Zagoren, J.C., Chen, S.M. and Suzuki, K.
Acta Neuropath. 29:141-156, 1974.

OBSERVED NEUROTOXIC EFFECTS: Scattered intracytoplasmic osmiophilic inclusions in central nervous system (far fewer than with Triparanol, q.v.) at higher dose-level only. No degeneration of oligodendroglia. Massive accumulations of desmosterol and less of $\Delta^{5,7,24}$-cholestatriene-3ß-ol. Authors argue that as a Δ^{7}-reductase inhibitor causes massive accumulations of 7-dehydrocholesterol (provitamin D_3), as $\Delta^{7,24}$ and $\Delta^{5,7,24}$ sterols produce Triparanol-like lesions, and as diazacholesterol produces few such lesions, the lesions may be due to a double bond at the 7-position.

ANIMALS: Rats, Wistar, M and F, newborn

PREPARATION AND DOSE or HISTORY OF PATIENT: 30 or 60 mg/kg/d in saline, from d 5 of age.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline only

DURATION OF EXPERIMENT: Serial, 15-32 d

EXAM. TYPE: Histology, biochemistry

54

COMPOUND: Androst-5-en-17-one, 3-beta-hydroxy-, succinate, sodium salt

REFERENCE: Heuser, G., Ling, G.M. and Buchwald, N.A.
Arch. Neurol 13:195-203, 1965.

OBSERVED NEUROTOXIC EFFECTS: Doses of 40-70 mg/kg produced sedation and slow wave activity. Doses of 100-150 mg/kg (high) resulted in repeated tonic seizures and intermittent falling spells.

ANIMALS: Monkeys, Squirrel, surgically prepared

PREPARATION AND DOSE
or HISTORY OF PATIENT: Varying doses approx 5-200 mg/kg.

ROUTE AND SITE: I.V. or I.P.

CONTROL INFORMATION: Sham inj as well as saline and sodium bicarbonate soln were used as controls. Control injections did not produce sedative or convulsion effects.

DURATION OF EXPERIMENT: Up to approx 30 min/test

EXAM. TYPE: Electrophysiology, behavior

COMPOUND: Aniline, 4,4'-sulfonyldi-

000080080

REFERENCE: duVivier, A. and Fowler, T.
Proc, Royal Soc. Med. 67:439-440, 1974.

OBSERVED NEUROTOXIC EFFECTS: Wasting of hand muscles and of some feet muscles. Sensorimotor neuropathy with denervation of small hand muscles with prolonged distal latency. Axonal degeneration and denervation atrophy. 4 mo. after withdrawal of dapsone, no recovery.

ANIMALS: 1 Human, M, age 57 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 200-300 mg/d for 18 yr for dermatitis herpetiformis. Complained of tingling of hands and feet and weakness of hands, starting 1 yr. before.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 18 yr. drug treatment, follow-up 4 mo.

EXAM. TYPE: Clinical, electromyography, nerve and muscle biopsy.

COMPOUND: o-Anisamide, 4-amino-5-chloro-N-(2-diethylamino)ethyl)-

REFERENCE: DeSilva, K.L., Muller, P.J. and Pearce, J.
Practitioner 211: 316-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Extrapyramidal signs, spasms especially of face, tongue and jaws, torticollis, opisthotonus, trismus; onset in 2-60 hrs. commonest in young. No dose relationship, recovery after withdrawal. One case had added diencephalic features. Authors comment that etiology still unknown, and suggest idiosyncracy to class of drugs (phenothiazines).

ANIMALS: Human: 10 cases, M & F, 14-30, selected from 20 cases treated at a hospital serving 500,000 population, over 2 yrs

PREPARATION AND DOSE or HISTORY OF PATIENT: 4 cases: 10 mg t.d.s., P.O.
Adverse drug reaction.

ROUTE AND SITE: t.d.s., P.O. (see above)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 12-48 hrs.

EXAM. TYPE: Clinical

COMPOUND: Anthraquinone, dihydroxy-

001322607

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115: 199-205, 1975

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus of colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

56

COMPOUND: Arsenic

007440382

REFERENCE: Chhuttani, P.N., Chawla, L.A. and Sharma, T.D.
Neurology 17:269-274, 1967.

OBSERVED NEUROTOXIC EFFECTS: Mainly sensory polyneuropathy, degeneration correlating in severity with clinical data, no specific pattern.

ANIMALS: Human: 34 M, 6 F aged 20-65 yr (av. 34.2) seen over 12 yr. in a series of 708 neuropathies (these were the cases due to As).

PREPARATION AND DOSE
or HISTORY OF PATIENT: Unknown amts. Sources: prescription 27, homicide 5, culinary 3, accident 3, injection 2.

ROUTE AND SITE: 30 Oral, 2 parenteral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 12yr

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Arsenic

007440382

REFERENCE: Hassin, G.B.
J. Nerv. Ment. Dis. 72:628-636, 1930.

OBSERVED NEUROTOXIC EFFECTS: Paralysis or polyneuritis of sudden onset deposits of arsenic seen as bands in nails, high arsenic content in hair.

ANIMALS: 6 Human case-reports

PREPARATION AND DOSE
or HISTORY OF PATIENT: Source, type and amount of arsenic intake not discovered.

ROUTE AND SITE: N.S.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Weeks to years

EXAM. TYPE: Clinical and laboratory

COMPOUND: Aspartic acid

REFERENCE: Olney, J.W. and Ho., O.
Nature 227:609-610, 1970.

OBSERVED NEUROTOXIC EFFECTS: Necrosis of hypothalamic neurons in mice given glutamate, compound or cysteine, dose-related; zero damage from other compounds

ANIMALS: 75 Mice, Swiss Webster, age 10 d.

PREPARATION AND DOSE or HISTORY OF PATIENT: One of 10 amino acids and various other compounds, 2.5 or 10% in water, 0.25-2 g/kg.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Intubated, no treatment, 10 mice

DURATION OF EXPERIMENT: 5 hr.

EXAM. TYPE: Histology

S7<

COMPOUND: Aspartic acid, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

58

COMPOUND: Aspartic acid, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, D-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuro-excitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Aspartic acid, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

59

COMPOUND: Aspartic acid, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Aspartic acid, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Aspartic acid, N-acetyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

61

COMPOUND: Aspartic acid, N-acetyl-, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

629

COMPOUND: Aspartic acid, N-carbamoyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Aspartic acid, N,N-dimethyl-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N,N-dimethyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

63

COMPOUND: Aspartic acid, N,N-dimethyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

94A

COMPOUND: Aspartic acid, N-ethyl, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-ethyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-ethyl, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

65

COMPOUND: Aspartic acid, N-formimino-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

66A

COMPOUND: Aspartic acid, N-iminomethyl-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-iminomethyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-methyl-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: Aspartic acid, N-methyl-, D- and D-homocysteic acid wer stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

>67<

COMPOUND: Aspartic acid, N-methyl, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Aspartic acid, N-methyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, alpha-methyl-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was toxic to non-neurol components (glia, etc.), but not to neurons.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Aspartic acid, N-methyl-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was more potent than monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

69

COMPOUND: Aspartic acid, N-methyl-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was more potent than monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Aspartic acid, N-methyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-propyl-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Aspartic acid, N-propyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

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ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Atropine

000051558

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Atropinium, 8-methyl-, nitrate

000052880

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 15 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Atropinium, 8-methyl-, nitrate

000052880

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced locomotor ataxia and arousal EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Atropine SO_4 (2:1)

000055481

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 40 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Atropine SO_4 (2:1)

000055481

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced locomotor ataxia and arousal EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2-10 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Barbituric acid, 5-allyl-5-(1-Methylbutyl)-

000076733

REFERENCE: Melville, K., Jordon, G., Douglas, D.
Toxicology and Applied Pharmacology 9:363-375, 1966.

OBSERVED NEUROTOXIC EFFECTS: Ataxia or "no spontaneous movement" as compared to intense central nervous system depression by synergistic action with alcohol.

ANIMALS: Mongrel dogs, 7.0-12.0 kg, M and F.

PREPARATION AND DOSE or HISTORY OF PATIENT: 25 mg/kg in total volume of 60 ml water

ROUTE AND SITE: Stomach tube

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: More than 1 wk.

EXAM. TYPE: Behavior

COMPOUND: Barbituric acid, 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)-, sodium salt

000309364

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 10-30 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Barbituric acid, 5,5-Diethyl-, sodium salt

000144025

REFERENCE: Essig, C.F. and Flanary, H.G.
Exp. Neurol. 3: 149-159, 1961.

OBSERVED NEUROTOXIC EFFECTS: Withdrawal caused major and minor seizures with bilaterally symmetrical inter-seizure EEG abnormalities. The cerebral cortex appeared to be involved, but only as secondary brainstem involvement.

ANIMALS: Cats, surgically prepared, 6

PREPARATION AND DOSE
or HISTORY OF PATIENT: Increasing doses, 95-335 mg/kg/d up to 267 d; then abrupt withdrawal

ROUTE AND SITE: Oral (capsules)

CONTROL INFORMATION: 3 cats prepared but untreated

DURATION OF EXPERIMENT: 106-267 d

EXAM. TYPE: Electrophysiological, behavioral

COMPOUND: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt (Nembutal)

000057330

REFERENCE: Becker, R.F., Flannagan, E. and King, J.E.
Neurology 8: 776-782, 1958.

OBSERVED NEUROTOXIC EFFECTS: Nembutal sedation of mother followed by Cesarian delivery resulted in severe neural damage. Of spontaneous deliveries after treatment with Nembutal on day 22, 42, or 63 of gestation, birth mortality was high; surviving young showed only mild signs of brain damage. Heavy anesthetization of newborn caused severe neuropathy.

ANIMALS: Guinea-pigs, pregnant

PREPARATION AND DOSE
or HISTORY OF PATIENT: 30 or 38 mg/kg before spontaneous delivery

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline; Cesarian section.

DURATION OF EXPERIMENT: term (average 66.5 d)

EXAM. TYPE: Teratology

COMPOUND: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt
000057330

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966.

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2-100 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-2-thio-, sodium salt
000071738

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10-30 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Barbituric acid, 5-ethyl-5-phenyl-

000050066

REFERENCE: Schain, R.J. and Watanabe, K.
Exp. Neurol. 47:509-515, 1975.

OBSERVED NEUROTOXIC EFFECTS: Body and brain growth retarded, not due only to impaired nutrition. In cerebellum, accumulation of cholesterol was retarded more than of DNA, RNA or protein, interpreted by authors as interference with myelination.

ANIMALS: Rats, Wistar, newborn M pups

PREPARATION AND DOSE
or HISTORY OF PATIENT: 30-60 mg/kg/d, from d 3-d 21, vehicle ns.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Littermate controls, vehicle only

DURATION OF EXPERIMENT: Sacr at 21 d age

EXAM. TYPE: Biochemical

COMPOUND: Benzamide, p-amino-n-(2-(diethylamino)ethyl))-

000051069

REFERENCE: Drachman, D.A. and Skom, J.H.
Arch. Neurol. 13:316-320, 1965.

OBSERVED NEUROTOXIC EFFECTS: Muscle weakness attributed to acetylcholine inhibition, recovered after withdrawal of compound on two occasions.

ANIMALS: 1 Human, M aged 78 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Myasthenia gravis with myocardial infarction on many drugs in hospital; single doses of 500 and 250 mg of compound, then 6 hourly doses of 250 mg for 14 doses.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 1 mo.

EXAM. TYPE: Clinical

COMPOUND: Benzenearsonic acid, 4-hydroxy-3-nitro-
000121197

REFERENCE: Wise, D.R., Hartley, W.J. and Fowler, N.G.
Res. Vet. Sci. 16: 336-340, 1974.

OBSERVED NEUROTOXIC EFFECTS: Those fed over 50ppm exhibited ataxic and leg weakness. No damage was found in the central nervous system, but distal peripheral nervous system degeneration (wallerian) of myelin and axons was observed.

ANIMALS: 75 Turkey hens, 1 d old, in 5 groups of 15

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0-547 ppm in diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated

DURATION OF EXPERIMENT: 35 d

EXAM. TYPE: Behavior, histology

COMPOUND: Benzilic acid, 1-methyl-3-piperidyl ester, hydrochloride

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 6 mg/man (experimental)
9 mg/man (hallucinogens)

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: 2-Benzimidazolinone, 1-(1-(3-(p-fluorobenzoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl)-
000548732

REFERENCE: DeSilva, K.L., Muller, P.J. and Pearce, J.
Practitioner 211: 316-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Extrapyramidal signs, spasms especially of face, tongue and jaws, torticollis, opisthotonus, trismus; onset in 2-60 hrs. commonest in young. No dose relationship, recovery after withdrawal. One case had added dienceph-alic features. Authors comment that etiology still unknown, and suggest idiosyncracy to class of drugs (phenothiazines).

ANIMALS: Human: 10 cases, M & F, 14-30, selected from 20 cases treated at a hospital serving 500,000 population, over 2 yrs

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 case: 10 mg. I.V.
Adverse drug reaction.

ROUTE AND SITE: I.V. (see above)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 3 hrs.

EXAM. TYPE: Clinical

COMPOUND: 3H-1,4-Benzodiazepine, 7-chloro-2-(methylamino)-5-phenyl-, 4-oxide

000058253

REFERENCE: Pearlman, C. and Becker, M.
Psychopharmacologia 42:63-66, 1975.

OBSERVED NEUROTOXIC EFFECTS: Cooperative behavior training and performance prevented when compound administered a few minutes after feeding session, no effects if given 3 hr afterwards. Authors concluded mechanism was prevention of REM sleep during this time.

ANIMALS: Rats: Long-Evans, F, 3 mo. age.

PREPARATION AND DOSE or HISTORY OF PATIENT: 4 mg/kg on alternate days a few minutes after session or after 3 hrs. of rest.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 6 Controls undistrubed sleep, 6 had saline inj. followed by normal sleep.

DURATION OF EXPERIMENT: Approx. 10 d

EXAM. TYPE: Behavior

COMPOUND: 3H-1,4-Benzodiazepine, 7-chloro-2-(methylamino)-5-phenyl-, 4-oxide

000058253

REFERENCE: Zbinden, G., Bagdon, R.E., Keith, E.F., Phillips, R.D., and Randall, L.O.
Toxicol. Appl. Pharmacol. 3: 619-637, 1961.

OBSERVED NEUROTOXIC EFFECTS: (1) Ingestion caused sedation, often ataxia and dysarthria, and in rare instances sleep and coma
(2 and 3) Symptoms similar to (1)

ANIMALS: (1) Human, 6 M and 16 F, 15 to 59 yr (attempted suicides)
(2) Rats, CFN
(3) Dogs

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 200 to 2250 mg/kg
(2) 20, 40, or 80 mg/kg/day for 52 wk
(3) 5 to 80 mg/kg/day for 6 mo

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 52 wk

EXAM. TYPE: Clinical

COMPOUND: 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-

006613850

REFERENCE: Greenblatt, D.J. and Kock-Weser, J.
Am. J. Med. Sci. 266: 261-266, 1973.

OBSERVED NEUROTOXIC EFFECTS: Apnea and coma, hypotension and coma, confusion and obtundation were observed in patients with contributory complications or other drug therapy.

ANIMALS: Human: 6 patients ages 40-91, 3.5% of 173 subjects given compound I.V., who were 1.2% of 2,623 patients receiving compound, who were 18.3% of 14,344 patients studied in a drug surveillance program.

PREPARATION AND DOSE or HISTORY OF PATIENT: Doses 5-30 mg/patient, one dose

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 19 d

EXAM. TYPE: Clinical

COMPOUND: Benzoic acid
000065850

REFERENCE: Kreis, H., Frese, K., and Wilmes, G.
Fd. Cosmet. Toxicol., 5: 505-511, 1967.

OBSERVED NEUROTOXIC EFFECTS: Retarded growth, irritation, ataxia, tonic-clonic convulsions. Necrosis of parenchymal cells of stratum granulosum of fascia dentata and cortex of lobus piriformis. Feeding of 1.1% failed to induce any neurotoxic signs or pathological changes in the brain.

ANIMALS: Rats, Weanling, M.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 3% dietary level for 5 d.
(2) 1.1% in diet for 35 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 5 d

EXAM. TYPE: Pathology, behavior

COMPOUND: Benzoic acid, p-amino-, 2-(diethylamino)ethyl ester (Procaine)
000059461

REFERENCE: Hirst, G.D.S. and Wood, D.R.
Br. J. Pharmac. 41: 94-104, 1971.

OBSERVED NEUROTOXIC EFFECTS: Procaine caused paralysis resembling that produced by tubocurarine. At low stimulation rates, it produced no depression of transmitter release but at high rates, a distinctive prejunctional failure was observed.

ANIMALS: Phrenic nerve-diaphragm preparations from rats, Wistar, M, 150-250 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.025-0.1 mM

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology

82A

COMPOUND: Benzoic acid, hydrazide
00613945

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.9 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Benzoxazole, 2-amino-5-chloro-
000061803

REFERENCE: Fujii, K., Jaffe, H. and Epstein, S.S.
Tox. Appl. Pharm. 13:431-438, 1968.

OBSERVED NEUROTOXIC EFFECTS: Temporary paralysis

ANIMALS: Mice, ICR Swiss Albino, A/J, and BALB/c

PREPARATION AND DOSE
or HISTORY OF PATIENT: 80 mg/kg as part of a larger study.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: 5 hr.

EXAM. TYPE: Clinical

COMPOUND: Benzyl alcohol, 3,4-dichloro-alpha-((isopropylamino)methyl)-, hydrochloride

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >50 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Benzyl alcohol, m-hydroxy-alpha-(methylamino)methyl)-, hydrochloride, (-)-
000061767

REFERENCE: Collinge, H.
Arch. Neurol. 3:656-660, 1960.

OBSERVED NEUROTOXIC EFFECTS: Polyneuropathy, severe disintegration of myelin in peripheral nerves and nerve roots.

ANIMALS: Human: 4 case reports; 1 case in addendum.

PREPARATION AND DOSE or HISTORY OF PATIENT: Furacin 0.5 g three times daily for 2 d, then four times daily for a total of 30.5 g; furadantin 100 mg four times daily for a total 24 g in 59 d; furandantin 100 mg four times daily for total of 18 g in 45 d (intermittent therapy). Addendum: furaltadone 250 mg four times daily for a total of 52 g in 26 d. (Furacin = Nitrofurazone; furadantin = nitrofurantoin)

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Months of follow-up

EXAM. TYPE: Behavior, autopsy

COMPOUND: Benzylamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-

000059961

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 33 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Benzylamine, N-methyl-N-2-propynyl-, hydrochloride

000306070

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 80 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Bicuculline

000485494

REFERENCE: Davidoff, R.A.
Science 175: 331-333, 1972.

OBSERVED NEUROTOXIC EFFECTS: The compound blocked the normal actions of GABA (gamma-aminobutyric acid)

ANIMALS: Frog spinal cord preparation, in vitro

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5 to 20 mcg/ml

ROUTE AND SITE: In vitro

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 10 hr

EXAM. TYPE: Electrophysiology

85

COMPOUND: Bicuculline

000485494

REFERENCE: Hill, R.G., Simmonds, M.A. and Straughan, D.W.
Br. J. Pharmac. 45: 176P-177P, 1972 (Abstract of proceedings).

OBSERVED NEUROTOXIC EFFECTS: The convulsive threshold was reached in 20 min; abnormal electrographs were seen before GABA antagonism, and were related with seizures. GABA was ineffective in preventing convulsions.

ANIMALS: Cats, surgically prepared

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20 mcg/min/kg

ROUTE AND SITE: I.V. infusion

CONTROL INFORMATION: Leptazol (6 mg) used as control

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry, behavior

COMPOUND: Bicuculline (Biculline)

REFERENCE: Johnston, G.A.R. and Mitchell, J.F.
J. Neurochem. 18:2441-2446, 1971.

OBSERVED NEUROTOXIC EFFECTS: All four compounds influenced the release of GABA, but not its uptake. Biculline at 10^{-5} M (not more or less) potentiated evoked release of GABA but not the resting release. Metrazol inhibited the electrically resting release but not the electrically evoked release. Strychnine and picrotoxin inhibited the electrically evoked release of GABA.

ANIMALS: In vitro slices of rat cerebral cortex

PREPARATION AND DOSE or HISTORY OF PATIENT: Preincubated with compounds for 15 min, then with labeled GABA for 10 min.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: 25 min

EXAM. TYPE: Biochemistry

COMPOUND: Biphenyl (Diphenyl)

000092524

REFERENCE: Hakkinen, I., Siltanen, E., Hernberg, S., Seppalainen, A.M., Karli, P. and Vikkula, E.
Arch. Env. Hlth. 26: 70-74, 1973.

OBSERVED NEUROTOXIC EFFECTS: There was evidence of central and peripheral nervous system damage. The damage to the peripheral nervous system was judged to be demyelination, while that of central nervous system appeared in an uncertain site affecting memory and temper as well as sensorimotor functions. The damage was progressive, with minor function recoveries, for observed 6-7 month follow-u after stopping exposure and the authors state that prognosis must await longer follow-ups.

ANIMALS: Human: 32 M, 1 F

PREPARATION AND DOSE or HISTORY OF PATIENT: History of exposure for various times to diphenyl in fruit paper manufacture. Case-reports of 1 fatal, 9 nonfatal cs exposed 5-15 yr to 4-128 mg/m^3 (measured in 1959) or 0.6-1 mg/m^3 (measured in 1970). TLV of 1 mg/m^3 was set in 1968, manufacturers claimed no dangers in paper-making in 1965. process involved 800-840 hr/yr exposure to 128 (1959) or 6 (1970) mg/m^3

ROUTE AND SITE: Inhalation and skin contact

CONTROL INFORMATION: None, and few data found in literature

DURATION OF EXPERIMENT: 5-15 yr with 6-7 mo follow-ups

EXAM. TYPE: History (ethanol and tri- and tetrachlorethylene solvents were eliminated), electromyography, EEG

COMPOUND: Biphenyl (Diphenyl)
000092524

REFERENCE: Seppalainen, A.M. and Hakkinen, I.
J. Neurol. Neurosurg, Psychiat. 38:248-252, 1975.

OBSERVED NEUROTOXIC EFFECTS: Abnormal EEG in 10, no recovery in 7 after 2 yr. Abnormal electromyographs in 9, fibrillation in 7. Reduced nerve conductions. These signs also persisted. Thus both central nervous system and peripheral nervous system were affected.

ANIMALS: Human: 23 M and 1 F selected from a larger group with industrial exposure.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Chronic, long term, to concentrations well over the TLV of 1 mg/m^3. Exposure ceased at start of study (after 1 fatality).

ROUTE AND SITE: Inhalation, skin contact, perhaps oral too.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 2 yr.

EXAM. TYPE: Clinical, electrophysiology

87<

COMPOUND: Biphenyl, chloro-

REFERENCE: Murai, Y. and Kuroiwa, Y.
Neurology 21:1173-1176, 1971.

OBSERVED NEUROTOXIC EFFECTS: Sensory neuropathy (symptoms and reduced conduction velocity) found in about one-half of the cases. Only one case of reduced motor conduction.

ANIMALS: 21 Humans, ages 7-60 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 21 consecutive cases seen at a hospital, in a mass outbreak of tetrachlorobiphenyl poisoning (total about 350 cases). Contaminated rice oil used for cooking.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Normal subjects were measured.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, electrophysiological

COMPOUND: Bis(p-aminophenoxy) alkane series

REFERENCE: Udall, V.
Proc. Roy. Soc. Med. 65: 197-199, 1972.

OBSERVED NEUROTOXIC EFFECTS: Retinal damage to pigmented epithelium, no pupil reflexes, perception deficits.

ANIMALS: Cats and Rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: ns

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Fundoscopy and histology

COMPOUND: Biuret, diamino-

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 3.0 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Boric acid

010043353

REFERENCE: Pfeiffer, C.C., Hallman, L.F. and Bersh, I.
J. Am. Med. Assn. 128:266-274, 1945.

OBSERVED NEUROTOXIC EFFECTS: Acute: antemortem rigidity of legs. The largest amount of boric acid was found in the brain: whole brain 214 mg/100 cc, cortex 231, corpus callosum 142 mg/100 cc. There was an increase of microglia, and a shrinkage of cord neurons. Cortex lesions were distributed through grey-matter in some, and concentrated around blood vessels in others. There was an accumulation in the brain after repeated doses.

ANIMALS: Dogs

PREPARATION AND DOSE or HISTORY OF PATIENT: Acute: 1.5-2 g/kg.

ROUTE AND SITE: Acute: S.C.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Boric acid

010043353

REFERENCE: Watson, E.H.
J. Am. Med. Assn. 129:332-333, 1945.

OBSERVED NEUROTOXIC EFFECTS: Fatal in 3 wk. Convulsions and coma, blindness, deafness. At autopsy "irreparable damage to the central nervous system" but brain not reported as examined.

ANIMALS: Human: M, age 4 1/2 mo., fatal case.

PREPARATION AND DOSE or HISTORY OF PATIENT: Eczema, treated with whole-body applications of compound, total estimated 60-100 g.

ROUTE AND SITE: Topical

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 3 wk.

EXAM. TYPE: Clinical

90<

COMPOUND: Boric acid, tri-o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: (1) All had paralysis. (2) All died.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C., (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Botulinum toxin type A

REFERENCE: Duchen, L.W.
Proc. Roy. Soc. Med. 65: 196-197, 1972.

OBSERVED NEUROTOXIC EFFECTS: The leg muscles were paralysed in 24 hours and recovered after 1 week. Progress and abnormalities in axonal regenerating sprouts were observed sequentially in time. The author concluded that the toxin binds either to the presynaptic axolemma or to a component of the motor nerve terminal axoplasm to block neuromuscular transmission; only new axonal tissue can transmit. Also concluded that the compound can induce the observed regeneration.

ANIMALS: Mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: "Sublethal" doses

ROUTE AND SITE: I.M., one hindleg

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Probably 6-7 d

EXAM. TYPE: Histology

COMPOUND: Botulinum toxin type A

REFERENCE: Holman, M.E. and Spitzer, N.C.
Br. J. Pharmac. 47: 431-433, 1973.

OBSERVED NEUROTOXIC EFFECTS: The toxin depressed or abolished transmission from postganglionic nerves to smooth-muscle, less rapidly than in rat diaphragm reported elsewhere.

ANIMALS: Isolated vas deferens preparations from mice and guinea-pigs

PREPARATION AND DOSE
or HISTORY OF PATIENT: Concentrations of compound ns

ROUTE AND SITE: Incubations in vitro

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Up to 6 hr

EXAM. TYPE: Electrophysiology

91^

COMPOUND: Botulinum toxin type A

REFERENCE: Simpson, L.L. and Rapport, M.M.
J. Neurochem. 18:1341-1343, 1971.

OBSERVED NEUROTOXIC EFFECTS: (1) Trisialoganglioside G_1 produced the solution with the least residual toxicity. (2) Survival time was prolonged in ratio to the amount of G_1; asialo-G_4-ganglioside was ineffective in vitro and in vivo as were sialic acid, glucose, galactose, galactosamine, or ceramide. (3) Potency for paralysing synaptic transmission was similarly diminished. Authors' conclusion: first demonstration of direct interaction of a compound with a natural constituent of nerve tissue.

ANIMALS: (1) In vitro incubation of toxin with test substances
(2) Residual toxicity tested in mice in vivo.
(3) Residual toxicity measured in vitro in rat phrenic nerve-diaphragm preparations.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Brain gangliosides singly or mixed 0.1-100 mcg incubation with compound type A at 10^3 or 10^4 MLD/ml.
(2) 10^4 MLD incubation, 0.1 ml of solution.
(3) as for (2).

ROUTE AND SITE: (1) In vitro (2) I.V. (3) Added to incubation mix in vitro.

CONTROL INFORMATION: (1) Without ganglioside.
(2) Without ganglioside, 10^3 MLD.
(3) Similar.

DURATION OF EXPERIMENT: (1) ns. (2) Over 300 min. (3) ns.

EXAM. TYPE: (1) Chemistry (2) Survival time (3) Physiology

92

COMPOUND: Br.sacodyl

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115:199-205, 1975.

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus of colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m.

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

COMPOUND: α-Bungarotoxin
11032794

REFERENCE: Katz, B. and Miledi, R.
Br. J. Pharmac. 49: 138-139, 1973.

OBSERVED NEUROTOXIC EFFECTS: The toxin inhibited acetylcholine sensitivity irreversibly but not the amplitude nor time-course of "elementary" potential changes.

ANIMALS: In vitro endplates of frog muscle fibers

PREPARATION AND DOSE or HISTORY OF PATIENT: Iontophoretic application

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: About 30 min

EXAM. TYPE: Electrophysiology

COMPOUND: 1,3-Butanediamine, N,N,N',N'-tetramethyl-

000097847

REFERENCE: Goldberg, M.E. and Johnson, H.E.
Tox. Appl. Pharm. 4:522-545, 1962.

OBSERVED NEUROTOXIC EFFECTS: This compound selectively blocked autonomic ganglia, and produced ocular disturbances.

ANIMALS: Rats, CFE, M, 5-6 wk old, 90-120 g, 5 rats/grp or 6/grp (inhalation)
Rabbits, NZ white, 2.5-3.5 kg, M, 4 rabbits/grp, and isolated ileum.
Mice, white, F, 20-28 g.
41 mongrel dogs (8.5-12.5 kg) M and F. 10 cats, F, 2.2-3.8 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various schedules

ROUTE AND SITE: Topical, shaved skin (rabbits); inhalation (rats, mice); intra-arterial (carotid) (dogs, cats) and I.V. femoral (dogs, cats)

CONTROL INFORMATION: Varied.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Physiology, biochemistry

93

COMPOUND: 1,4-Butanediol

0001110634

REFERENCE: Zabik, J.E., Van Dam, D.P. and Maickel, R.P.
Res. Comm. Chem. Path. Pharm. 8(1):83-90, 1974.

OBSERVED NEUROTOXIC EFFECTS: Loss of righting reflex, assumed to show toxicity. This reflex was reduced, dose-dependent, from 50 mg/kg on up, with complete loss at 300 and 400 mg/kg. No increase in triglycerides (metabolic).

ANIMALS: Rats, S-D, M, 300-350 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-1600 mg/kg/d, 1-14 doses. 1600 mg/kg was LD_{100}, 1328 mg/kg was LD_{50}, no deaths below 1000 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, metabolism

COMPOUND: 1,3-Butanediamine, N,N,N',N'-tetramethyl-

000097847

REFERENCE: Goldberg, M.E. and Johnson, H.E.
Tox. Appl. Pharm. 4:522-545, 1962.

OBSERVED NEUROTOXIC EFFECTS: This compound selectively blocked autonomic ganglia, and produced ocular disturbances.

ANIMALS: Rats, CFE, M, 5-6 wk old, 90-120 g, 5 rats/grp or 6/grp (inhalation)
Rabbits, NZ white, 2.5-3.5 kg, M, 4 rabbits/grp, and isolated ileum.
Mice, white, F, 20-28 g.
41 mongrel dogs (8.5-12.5 kg) M and F. 10 cats, F, 2.2-3.8 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: Various schedules

ROUTE AND SITE: Topical, shaved skin (rabbits); inhalation (rats, mice); intra-arterial (carotid) (dogs, cats) and I.V. femoral (dogs, cats)

CONTROL INFORMATION: Varied.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Physiology, biochemistry

63

COMPOUND: 1,4-Butanediol

0001110634

REFERENCE: Zabik, J.E., Van Dam, D.P. and Maickel, R.P.
Res. Comm. Chem. Path. Pharm. 8(1):83-90, 1974.

OBSERVED NEUROTOXIC EFFECTS: Loss of righting reflex, assumed to show toxicity. This reflex was reduced, dose-dependent, from 50 mg/kg on up, with complete loss at 300 and 400 mg/kg. No increase in triglycerides (metabolic).

ANIMALS: Rats, S-D, M, 300-350 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-1600 mg/kg/d, 1-14 doses. 1600 mg/kg was LD_{100}, 1328 mg/kg was LD_{50}, no deaths below 1000 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, metabolism

COMPOUND: 2-Butanol,4-(dimethylamino)-3-methyl-1,2-diphenyl-, propionate (ester), hydrochloride (+)-

001639607

REFERENCE: Chapman, J.E. and Walaszek, E.J.
Tox. Appl. Pharm. 4:752-758, 1962.

OBSERVED NEUROTOXIC EFFECTS: The LD_{50} of this compound, when given i.p., was 68-105 mg/kg. Convulsions produced and shown to be of cerebral origin.

ANIMALS: Rats, Holtzman, F, 200 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 10-160 mg/kg with/without nalorphine; Some rats were prepared surgically-spinal cord sectioned.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Antagonist or no controls.

DURATION OF EXPERIMENT: Observed until death or recovery.

EXAM. TYPE: Behavior, mortality.

COMPOUND: 2-Butanol, 4-(dimethylamino)-3-methyl-1,2-diphenyl-, propionate (ester) hydrochloride (+)-
001639607

REFERENCE: Young, D.J.
Arch. Int. Med. 129:62-66, 1972.

OBSERVED NEUROTOXIC EFFECTS: Tissue levels reached 130 mg/kg in brain where measured. Convulsions and respiratory arrest. Blood levels miniscule. Death resulted from anoxia and complications. Central nervous system stimulation hypothesized by author.

ANIMALS: Human: 10 cases, 9 suicides and 1 survival (3M, 7 F)

PREPARATION AND DOSE or HISTORY OF PATIENT: Doses of 1-2 g where known.

ROUTE AND SITE: Oral None

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Pathology (gross), behavior

COMPOUND: Butyl alcohol

000071363

REFERENCE: Roach, M.K., Davis, D.L. Pennington, W. and Nordyke, E.
Life Sci. 12(1):433-441, 1973.

OBSERVED NEUROTOXIC EFFECTS: Butanol inhibited active transport of probable neurotransmitters of the central nervous system by synaptosomes. Authors conclude that alcohol interacts with membrane lipids of synaptosome.

ANIMALS: Rats, S-D, M, 200-250 g, brains removed and homogenates incubated in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: Butanol added as 25% soln, at start of preincubation period. Butanol conc 5-30 mg/ml. Incubated in vitro with labeled norepinephrine, GABA and glutamate.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Control: incubation in medium with no alcohol.

DURATION OF EXPERIMENT: Laboratory procedure

EXAM. TYPE: Biochemistry

COMPOUND: Butyric acid, 4-amino

000056122

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

96

COMPOUND: Butyric acid, 2-amino-4-hydroxy-, phosphonate, (ester)

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was toxic to non-neurol components (glia, etc.), but not to neurons.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Butyric acid, 2-amino-4-sulfino-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Butyric acid, 2-hydrazino-2-methyl-

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.52 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

97

COMPOUND: Butyric acid, 2-(methylamino)-4-sulfo-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

98

COMPOUND: Cadmium chloride

010108642

REFERENCE: Gabbiani, G., Baic, D. and Daziel, C.
Exp. Neurol. 18:154-160, 1967.

OBSERVED NEUROTOXIC EFFECTS: Hemorrhagic damage, especially to granular layer of cerebellum, also cerebrum, but only in young rats and rabbits.

ANIMALS: Rats, aged 1-30 d, 5 groups of 10 (S-D)
Rabbits, 43, aged 1-30 d

PREPARATION AND DOSE
or HISTORY OF PATIENT: Rats: 10 mg/kg
Rabbits: 20 mg/kg

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 2 rats/1 rabbit per group untreated.

DURATION OF EXPERIMENT: 30 d mentioned, real duration ns.

EXAM. TYPE: Histology

COMPOUND: Cadium chloride

010108642

REFERENCE: Gabbiani, G., Gregory, A. and Baic, D.
J. Neuropath. Exp. Neurol. 26(3):498-506, 1967.

OBSERVED NEUROTOXIC EFFECTS: Acute hemorrhagic lesions of Gasserian and sensory spinal ganglia in all species. Nuclear pyknosis, PAS - and H-positive masses in nerve fibers. Pretreatment with zinc acetate or glutathione protected the animals.

ANIMALS: Guinea-pigs, golden hamsters, and mice in grps of 10; 260 rats: S-D, 205 g, in grps of 15. 3 grps of rats also had surgical transection of the spinal cord, right sciatic and femoral nerves.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg in water (1 ml/inj); rats given 2 mg/rat in 1 ml of water.

ROUTE AND SITE: S.C., interscapular region

CONTROL INFORMATION: 20 rats untreated

DURATION OF EXPERIMENT: 1-96 hr

EXAM. TYPE: Behavior, histology

COMPOUND: Cadmium chloride

010108642

REFERENCE: Tischner, K.H. and Schroder, J.M.
J. Neurol. Sci. 16:383-399, 1972.

OBSERVED NEUROTOXIC EFFECTS: Glycogen deposits in periphery of neuronal perikarya, dose-related. Other ultrastructural changes including mitochondria and unmyelinated axons (degeneration). Authors conclude that cadmium ions are direct pathogens for nerve tissues.

ANIMALS: Dorsal root ganglia from 19-21 d Wistar rat embryos in culture.

PREPARATION AND DOSE or HISTORY OF PATIENT: 4×10^{-4} M in medium, replenished every 3 d, exposures 1 d to 3 wk.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: no.

DURATION OF EXPERIMENT: Cultures maintained up to 2 mo.

EXAM. TYPE: Histology, chemistry

COMPOUND: Caffeine

000058082

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: 84.4 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: na

EXAM. TYPE: Clinical

100

COMPOUND: Calcium chloride

010043524

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: The compound did not antagonize the effects of lincomycin.

ANIMALS: 3 rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-50 mg/kg during the neuromuscular blockade produced by lincomycin.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

COMPOUND: Carbamic acid, diethylthio-, sodium salt

REFERENCE: Edington, N. and Howell, J. McC.
Nature 210:1060-1062, 1966.

OBSERVED NEUROTOXIC EFFECTS: Copper level in the CNS was increased by compound, not by saline. Cord white matter had Wallerian degeneration throughout, loss of structure in some grey-matter neurons. Corpus striatum not damaged. Some sciatic nerves also contained Wallerian degeneration.

ANIMALS: 18 Rabbits, Dutch and NZ

PREPARATION AND DOSE or HISTORY OF PATIENT: Dose ns., but after 5 mo. it was 10 ml/kg/d, in 15 rabbits for a further 2.5 mo.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 3 given saline, 5 ml/kg/d.

DURATION OF EXPERIMENT: Approx 7.5 mo.

EXAM. TYPE: Histology, biochemistry

COMPOUND: Carbamic acid, diethyldithio-, sodium salt

REFERENCE: Edington, N. and Howell, J. McC.
Acta Neuropath. 12:339-347, 1969.

OBSERVED NEUROTOXIC EFFECTS: Degeneration: at 6 wk in accessory cuneate nucleus and Clarke's column, at 18 wk in spinocerebellar tracts of cerebellum and in medulla, at 24 wk in peripheral white-matter of cord. Peripheral Nervous System effects "minimal."

ANIMALS: 25 Rabbits, (Dutch x NZ), M and F, 2.6-3.3 kg in 5 grps of 5.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 330 mg/kg/d, 6 d/wk, in buffer to all 5 grps.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 6-30 wk.

EXAM. TYPE: Histology

101^

COMPOUND: Carbamic acid, diethylthio-, sodium salt

REFERENCE: Howell, J. McC. and Edington, N.
J. Neuropath. Exp. Neurol. 27:464-472, 1968.

OBSERVED NEUROTOXIC EFFECTS: Wallerian nerve fiber degeneration in cerebellum, medulla, cord, and peripheral nerves.

ANIMALS: 13 Hens, Thornber's 404 strain, age 6 mo.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 330 mg/kg/d, 5 d/wk, as 10% solution in phosphate buffer pH 7.2-7.4 (7 hens).

ROUTE AND SITE: Deposited in crop

CONTROL INFORMATION: 4 hens given saline in buffer

DURATION OF EXPERIMENT: 19 wk

EXAM. TYPE: Histology

1 1

102

COMPOUND: Carbamic acid, diethylthio-, sodium salt

REFERENCE: Howell, J. McC., Ishmael, J., Ewbank, R. and Blakemore, W.F. Acta Neuropath. 15:197-207, 1970.

OBSERVED NEUROTOXIC EFFECTS: No signs of incoordination. All lambs had peritonitis. Microscopic lesions in medulla and spinal cord: swollen axons but no nerve fiber degeneration. High copper levels found in spinal cord.

ANIMALS: Sheep, 20 Clun Forest purebreds or crosses, 5 aged 2 d, 11 aged 1 mo.

PREPARATION AND DOSE or HISTORY OF PATIENT: 165 or 330 mg/kg in phosphate buffer pH 7.0, daily 5 d/wk.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: [illegible]ed 2 d, vehicle only

DURATION OF EXPERIMENT: One survivor and the controls sacr at 16 wk.

EXAM. TYPE: Histology, behavior, biochemistry.

COMPOUND: Carbamic acid, diethylthio-, sodium salt

REFERENCE: Rasul, A.R. and Howell, J.McC. Acta Neuropath. 24:68-75, 1973.

OBSERVED NEUROTOXIC EFFECTS: Degeneration of the long tracts of the spinal cord: fragmented axons and ballooned myelin sheaths. Lesions could be traced into cerebellum. Lesions were first seen after 18 wk in chicks and 4 wk in adults. Ataxia was observed after 25 wk in chicks and 5 wk in adults. Degeneration characterized as a "dying back process" and an "organophosphorous pattern."

ANIMALS: Cockerels, Thornber's 909, aged 1 wk or 6 mo.

PREPARATION AND DOSE or HISTORY OF PATIENT: 330 mg/kg/d, 6 d/wk, in phosphate buffer

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated birds

DURATION OF EXPERIMENT: Serial to 35 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Carbamic acid, diethyldithio-, sodium salt
000148185

REFERENCE: Rasul, A.R. and Howell, J. McC.
Acta Neuropath. 24:161-173, 1973.

OBSERVED NEUROTOXIC EFFECTS: No effects on neuromuscular endplates, peripheral nerves, or "teased" nerve fibers. Treatment for 9 wk, fewer large-diameter fibers. In central nervous system: Wallerian degeneration and eosinophilic bodies seen after 4 wk of treatment; long spinal tracts involved, initial lesions inferred in thoracic cord.

ANIMALS: 20 Rabbits, Dutch, M, 12 wk, 1.88-2.48 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 330 mg/kg/d, 5-d/wk as 10% soln in NaPO buffer pH 7.2-7.4

ROUTE AND SITE: Oral

CONTROL INFORMATION: 10 rabbits NaPO buffer only.

DURATION OF EXPERIMENT: Serial sacr 4,6,9 wk.

EXAM. TYPE: Histology

103<

COMPOUND: Carbamic acid, ethyl ester
000051796

REFERENCE: Ferm, V.H.
Arch. Path. 81: 174-177, 1966.

OBSERVED NEUROTOXIC EFFECTS: Exencephaly and failure of neural tube to close after administration of compound, more so after I.V. treatment.

ANIMALS: Golden hamsters, F, pregnant, 100-125 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 25-150 mg/hamster on d 9, 10 or 11

ROUTE AND SITE: I.V. lingual vein or I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24-72 hr. after treatment.

EXAM. TYPE: Teratological

104

COMPOUND: Carbamic acid, dimethyl-6-methyl-2-propyl-4-pyrimidnyl ester

002592492

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 60.0 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Carbamic acid, methyl-, benzo(b)thien-4-yl-ester

0010793310

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 400 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Carbamic Acid, methyl-, benzo(b)thien-4-yl-ester
001079330

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 85.4 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

105

COMPOUND: Carbamic acid, methyl-, S-sec-butyl-2-chlorophenyl ester
002917193

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 19.4 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

106

COMPOUND: Carbamic acid, methyl-m-sec-butylphenyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 13.6 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 1 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Carbamic acid, methyl-, m-cumenyl ester

000064006

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 12.0 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Carbamic acid, methyl-,2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester

001563662

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 6.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

<207

COMPOUND: Carbamic acid, methyl-,4-dimethyl-amino-3,5-xylyl ester

000315184

REFERENCE: Tucker, R.K. and Crabtree, D.G.
J. Econ. Entomol. 62:1307-1310, 1969.

OBSERVED NEUROTOXIC EFFECTS: Varying with the species the following symptoms were observed: Tachypnea, ataxia, tremors, salivation, lachrimation, piloerection, clonic or tonic convulsions, opisthotonus, phonation, anorexia, nystagmus. Death tended to follow respiratory paralysis. Birds were generally more susceptible than mammals; cumulative effects were not marked; teratology was not demonstrated; the authors concluded that practical exposures would be far below toxic levels.

ANIMALS: Rats (S-D), Rabbits (NZ White), Lesser sandhill cranes, Canada geese, Mourning doves, Mallard ducks, Coturnix quails, Ring-necked pheasants, House finches, Chukar partridges, Domestic pigeons, Sharp-tailed grouse, Domestic goats, Mule deer, House sparrows, Bullfrogs.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Acute oral LD_{50} varied from 1 mg/kg in cranes to 800 mg/kg in bullfrogs. Subacute feeding tests at various doses. Acute dermal toxicity tests in rabbits, 2 g/kg.

ROUTE AND SITE: Oral; dermal

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Subacute, 30 d.

EXAM. TYPE: Behavior, mortality

108

COMPOUND: Carbamic acid, methyl-, m-(1-methylbutyl)phenyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 44.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Carbamic acid, methyl-, 1-naphthyl ester

000063252

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 800 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Carbamic acid, methyl-, 1-naphthyl ester
000063252

REFERENCE: Smalley, H.E., O'Hara, P.J., Bridges, C.H. and Radeleff, R.D.
Tox. Appl. Pharm. 14:409-419, 1969.

OBSERVED NEUROTOXIC EFFECTS: Myasthenia, incoordination, ataxia, tremor, clonic contractions, paraplegia. Compound inhibits cholinesterase. Central nervous system lesions: edema of myelinated tracts of cerebellum, brain stem, and upper cord, with vascular degeneration.

ANIMALS: Pigs, Yorkshire, litter of 4 M and 4 F, in 2 groups.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 150 and 300 mg/kg/d in diet.

ROUTE AND SITE: Oral, incidental inhalation

CONTROL INFORMATION: 2 pigs of litter

DURATION OF EXPERIMENT: Up to 85 d

EXAM. TYPE: Clinical, histology

COMPOUND: Carbamic acid, methyl-, 3,4-5-trimethylphenyl ester
002686999

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 400 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

110

COMPOUND: Carbamic acid, methyl-,3,4-5-trimethylphenyl ester

002686999

REFERENCE: Sherman, H., Herrick, R.B., Ross, E. and Chang, M.T.Y. Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 50.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Carbohydrazide

000497187

REFERENCE: Jenney, E.H. and Pfeiffer, C.C. J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1.3 mM/kgm

ROUTE AND SITE: I.V.

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Carbohydrazide, thio-

000231574

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.04 ml/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

111

COMPOUND: Carbon dioxide

000124389

REFERENCE: Walker, J.L., Jr. and Brown, A.M.
Science 167:1502-1504, 1970.

OBSERVED NEUROTOXIC EFFECTS: Some neurons were depolarized, others hyperpolarized, others unaffected. Mechanism: acidosis that increased membrane chloride conductance of responsive cells.

ANIMALS: Aplysia californica surgically prepared.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Abdominal ganglion exposed to 5% CO_2.

ROUTE AND SITE: Laboratory methods described.

CONTROL INFORMATION: Described

DURATION OF EXPERIMENT: About 1 min.

EXAM. TYPE: Electrophysiology

112<

COMPOUND: Carbon disulfide
000075150

REFERENCE: Alpers, B.J. and Lewy, F.H.
Arch. Neurol. Psychiat. 44:725-739, 1940.

OBSERVED NEUROTOXIC EFFECTS: Apathy, hostility. Damage to cortex, basal ganglia, cerebellum; moderate involvement of cord; little involvement of brainstem and peripheral nervous system.

ANIMALS: 9 Dogs

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure 8 hr/d, 5 d/wk, for 2-6 wk. Concentration ns.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 2-6 wk.

EXAM. TYPE: Behavior, Histology

COMPOUND: Carbon disulfide
000075150

REFERENCE: Ferraro, A., Jervis, G.A., & Flicker, D.J.
Arch. Pathol. 32: 723-738, 1941.

OBSERVED NEUROTOXIC EFFECTS: Cerebrovascular proliferation with diffuse nerve cell changes (from chrolatolysis to severe degeneration) scattered through brain and cerebellum. Salivation, dyspnea, restlessness, rarely vomiting, progressing to tremors, apathy, and occasionally coma.

ANIMALS: 5 Cats.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 8-10 mg/liter of air, 0.5-2.5 hr/d, total exposures 19-65

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr to 92 d

EXAM. TYPE: Behavior, histology

COMPOUND: Carbon disulfide

000075150

REFERENCE: Juntunen, J., Haltia, M. and Linnoila, I.
Acta Neuropath. 29:361-366, 1974.

OBSERVED NEUROTOXIC EFFECTS: Slight weakness, progressing to severe in hindlimbs. Only intramuscular nerves examined: axonal degeneration. Intense nonspecific cholinesterase activity correlated with degeneration. Authors suggest that non-specific cholinesterase activity could be used as an indicator of early axonal degeneration in progressive polyneuropathy.

ANIMALS: 21 Rats, S-D, age 3 mo.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 750 ppm in air, 6 hr/d for 5 d/wk or (later) 3/d/wk.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: 5 rats untreated

DURATION OF EXPERIMENT: 5 wk to 5 mo.

EXAM. TYPE: Behavior, histology, histochemistry

1137

COMPOUND: Carbon disulfide

000075150

REFERENCE: Lewey, F.H.
Ann. Int. Med. 15: 869-883, 1941.

OBSERVED NEUROTOXIC EFFECTS: Any part of the central or peripheral nervous system can be affected. In general, the first signs were psychic with peripheral neuropathy, progressing to cranial nerve involvement, eye muscle control, pyramidal and extra-pyramidal signs. Parkinsonism and a thalamic syndrome were seen. The author concluded that some neuropathy was secondary to induced thiamine deficiency.

ANIMALS: Human: 120 viscose rayon workers

PREPARATION AND DOSE
or HISTORY OF PATIENT: Long-term chronic exposures

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical, biochemistry, statistics

114

COMPOUND: Carbon disulfide
000075150

REFERENCE: Lukas, E., Kotas, P. and Obrusnik, I.
Br. J. Indust. Med. 31: 288-291, 1974.

OBSERVED NEUROTOXIC EFFECTS: Slow conduction measured in lumbar plexus-tibial nerves. Copper levels increased, while zinc did not.

ANIMALS: Rats, SPF, M, 300 g, 18/gp, 2 gps trtd.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2.4 or 3.6 mg/liter of air, 6 hr/d, 5 d/wk.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Same numbers of rats.

DURATION OF EXPERIMENT: Sacrifice when neuropathy obvious (13 or 37 wk).

EXAM. TYPE: Electrophysiology, biochemistry.

COMPOUND: Carbon disulfide
000075150

REFERENCE: Richter, R.
J. Neuropath. Exp. Neurol. 4:324-353, 1945.

OBSERVED NEUROTOXIC EFFECTS: Grey-matter necrosis especially in globus pallidus and substantia nigra, thought to have developed acutely after long cumulative exposures; other changes such as gliosis in nonnecrotic parts of Central Nervous System thought to have developed gradually.

ANIMALS: 4 Rhesus monkeys (M. mulatta), healthy, young.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure to vapor, concentration not measured, for about 6 hr/d, 5 d/wk, for 1-2 yr.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1-2 yr.

EXAM. TYPE: Behavior, histology

COMPOUND: Carbon disulfide

000075150

REFERENCE: Tarkowski, S. and Cremer, J.E.
J. Neurochem. 19:2631-2640, 1972.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, tremors, some convulsions; brain glutamine rose, glutamate and GABA fell, interpreted as due to increased removal of ammonia and interference with pyridoxal-PO_4-dependent enzymes.

ANIMALS: Rats, Porton, M, 8-10 wk, 180-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 2.5 mg/liter of air for 15 hr.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Same, no compound

DURATION OF EXPERIMENT: 15 hr.

EXAM. TYPE: Behavior, biochemistry

EPA

COMPOUND: Carbonic acid, dithio-, cyclic S,S-(6-methyl-2,3-quinoxalinediyl) ester

REFERENCE: Sherman, H., Herrick, R.B., Rose, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 979.6 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

116

COMPOUND: Carbon monoxide

000630080

REFERENCE: Sogusr, M., Cholewa, L. Pach, J. and Mlodkowska, F.
Arch. Toxicol. 33:141-149, 1975.

OBSERVED NEUROTOXIC EFFECTS: Lactate, pyruvate, aspartate aminotransferase, LDH, all increased; muscle twitching to convulsions. A triple-normal lactate was considered reason for hospitalization, and triple-normal Asp-At signified complications.

ANIMALS: 47 patients: 28 F, 19 M, ages 14-88 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to coal-stove gas or lighting gas for 1-16 hr, hospitalized 1-5 hr after onset of symptoms.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, biochemistry

COMPOUND: Carbon monoxide

000630080

REFERENCE: Einhorn, I.N.
Env. Hlth. Persp. 11:163-189, 1975.

OBSERVED NEUROTOXIC EFFECTS: Level 3 (motor collapse): no changes observable in central or peripheral nervous system by light microscopy in 10 rats exposed 30 d, but on electron microscope changes seen in Ranvier nodes in peripheral nervous system. Demyelination apparent at level 4, especially of large fibers in central nervous systems white-matter.

ANIMALS: Rats

PREPARATION AND DOSE or HISTORY OF PATIENT: Levels 2-5 of toxicity produced by various exposures.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, histology, behavior

COMPOUND: Carbon monoxide

000630080

REFERENCE: Shillito, F.H., Drinker, C.K. and Shaughnessy, T.J.
J. Am. Med. Assn. 106: 669-674, 1936.

OBSERVED NEUROTOXIC EFFECTS: 43 cases had sequelae sufficient for admission to mental institutions; confusion psychosis, disorientation, amnesia, parkinsonism, increased deep reflexes, skin anesthesia and peripheral neuropathy. All such cases had unconsciousness during acute phase, none had low-level chronic exposures. Of the 43, 23 recovered completely, 9 had permanent nerve or mental damage, and 11 died.

ANIMALS: Human: 43 cases abstracted from 10-yr records of 21,143 cases in New York metropolitan area

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various exposures

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Clinical

11272

COMPOUND: Carbon monoxide

000630080

REFERENCE: Snyder, R.D.
Neurology 20:177-180, 1970.

OBSERVED NEUROTOXIC EFFECTS: Symmetrical peripheral neuropathy not due only to hypoxia, additional to Central Nervous system involvement, suspected of "toxic or ischemic basis."

ANIMALS: Human: family of 4 (M 25 yr, F 29 yr, M 5 yr, F 3 yr).

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure to malfunctioning gas heaters in closed house, for approx. 2 d.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 2 d

EXAM. TYPE: Autopsy (F, 29), electrophysiology, blood chemistry, behavior

118

COMPOUND: Carbon tetrachloride

000056235

REFERENCE: Cohen, M.M.
Neurology 7: 238-244, 1957.

OBSERVED NEUROTOXIC EFFECTS: The compound caused patchy pontine necrosis and demyelination and Purkinje cell damage; other effects were considered secondary to vascular, hepatic or renal damage.

ANIMALS: Human: 2 fatal cases, M, 24 and 40

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) A suicide; history of alcohol, drugs and liver damage.
(2) Accidental inhalation; history of alcohol

ROUTE AND SITE: (1) Oral (2) Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: (1) Survived 13 d; (2) survived less than 24 hr

EXAM. TYPE: Histology (autopsy)

COMPOUND: Carbon tetrachloride

000056235

REFERENCE: Hasson, J. and Leech, R.W.
Arch. Path. 84:286-289, 1967.

OBSERVED NEUROTOXIC EFFECTS: Globus pallidus was examined; Alzheimer glia cell changes were not found, but astrocytic nuclear size was increased significantly in cirrhotic vs. control rats.

ANIMALS: Rats, S-D, M, 150 g, 2 groups of 18

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 ml/kg twice/wk for 5 wk (10 doses), 1 group, to produce liver cirrhosis.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: 1 group untrtd

DURATION OF EXPERIMENT: Sacrifice 1 d after 10th dose.

EXAM. TYPE: Histology

COMPOUND: Carbon tetrachloride

000056235

REFERENCE: Knott, P.J. and Curzon, G.
Biochem. Pharmacol. 24:963-966, 1975.

OBSERVED NEUROTOXIC EFFECTS: Brain tryptophan, tyrosine, 5-HIAA and (less) 5-HT increased; related decrease of food intake. Brain changes not seen with restricted intake alone. Interpreted with reference to appetite control and liver failure.

ANIMALS: Rats, S-D, M, 140-150 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 10% in arachis oil, 13 ml/kg when mean wt was 200 g, one dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Arachis oil vehicle only; restricted diet 48 hr.

DURATION OF EXPERIMENT: 48 hr.

EXAM. TYPE: Biochemical

119A

COMPOUND: Carbon tetrachloride

000056235

REFERENCE: Luse, S.A. and Wood, W.G.
Arch. Neurol. 17:304-312, 1967.

OBSERVED NEUROTOXIC EFFECTS: Mental stupor, confusion, convulsion. Edema and spongiform lesions through pons, cerebellum, cerebrum. No demyelination by electronmicroscopy, though appearance of it by photomicroscopy. Edema was extracellular.

ANIMALS: Human: one case, M, 32

PREPARATION AND DOSE or HISTORY OF PATIENT: Used a CCl_4 extinguisher for a fire in a closed room. Died 7 d later, without reporting this.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 7 d

EXAM. TYPE: Behavior, clinical, histology

120

COMPOUND: Cardiotoxin

REFERENCE: Chang, C.C., Chuang, S-T., Lee, C.Y., Wei, J.W.
Br. J. Pharmac. 44:752-764, 1972.

OBSERVED NEUROTOXIC EFFECTS: Affected axonal conduction, but less potent than crude cobra venom. Blocking action accelerated by addition of PhA, the minimum effective concentration being 100 mcg/ml. 3 mcg/ml completely depolarized superficial muscle fibers within 60 min, this dose being three times more potent than crude venom. $CaCl_2$ antogonized nerve blocking and depolarizing effect.

ANIMALS: Phrenic nerve-diaphragm preparation from Long-Evans rats.

PREPARATION AND DOSE or HISTORY OF PATIENT: Various doses in vitro.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, chemistry

COMPOUND: Cascara

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115:199-205, 1975.

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus of colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m.

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

COMPOUND: beta-Chloroethylamine, ethyl-n-propyl-, hydrochloride

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B. J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic β-chloroethylamines but not when (a) OH or bromine replaced the β chlorine, (b) a β-phenyl group replaced one of the β hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary β-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-β-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

1:1<

COMPOUND: Choralose, alpha

015879933

REFERENCE: Spooner, C.E. and Winters, W.D. Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 20-50 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

122

COMPOUND: Citric acid, fluoro-

REFERENCE: Koenig, H.
Science 164:310-312, 1969.

OBSERVED NEUROTOXIC EFFECTS: Convulsions. Cord neurons expelled lysosomes, mitochondria, other cytoplasmic structures into their axons. Axons and mitochondria swelled.

ANIMALS: Cats

PREPARATION AND DOSE or HISTORY OF PATIENT: 3-50 mcg of active isomer in 0.003-0.05 ml water, one dose.

ROUTE AND SITE: Inj. into lumbar subarachnoid space

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr up to 24 hr, av 1-6 hr.

EXAM. TYPE: Behavior, histology

COMPOUND: Citric acid, fluoro-

REFERENCE: Patel, A. and Koenig, H.
J. Neurochem. 18: 621-628, 1971.

OBSERVED NEUROTOXIC EFFECTS: Fluorocitrate blocks citrate (isocitrate) hydrolyase (EC 4.2.1.3); before and during convulsions, rat brain and cat spinal cord alanine rose, and free aspartate, glutamate and glutamine fell; GABA rose, then fell; citrate rose markedly; glycogen fell; ammonia and ATP remained constant; incorporation of glucose and lysine into nerve proteins fell sharply. The authors propose that convulsions follow complexing of excess citrate with Mg^{++} and consequent chemical reactions.

ANIMALS: Rats, S-D, F, 180-200 g
Cats, adult, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 1.5 mcg/rat
10 mcg/cat

ROUTE AND SITE: Rats, intracerebral; cats, into lumbar subarachnoid space

CONTROL INFORMATION: Compound omitted from treatment

DURATION OF EXPERIMENT: Rats 20 min, cats 30 min

EXAM. TYPE: Biochemistry

COMPOUND: Cobalt ion (+2)

REFERENCE: Nichols, R.A. and Nakajima, Y.
Brain Res. 86: 493-498, 1975

OBSERVED NEUROTOXIC EFFECTS: Cobalt inhibited the generation of the IPSP (sic) of the stretch receptor neuron and had some depolarizing action on the soma.

ANIMALS: In vitro: slow adapting stretch receptors from 8th thoracic segment of lobster (H. americanus) and crayfish (Oronectes), or from the 2nd-3rd abdominal segment of crayfish.

PREPARATION AND DOSE or HISTORY OF PATIENT: Co at 0-5 mM

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Zero treatment

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Cobalt ion (+2)

REFERENCE: Prakash, N.J., Fontana, J. and Henkin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: Inhibited ($Na^+ + K^+$) ATPase, although never more than 20%, even at 0.2 mM. Inhibition involved blockage of norepinephrine and choline uptake.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Co^{++} chloride added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

124

COMPOUND: Cobra toxin

REFERENCE: Chang, C.C., Chuang, S-T., Lee, C.Y., Wei, J.W.
Br. J. Pharmac. 44:752-764, 1972.

OBSERVED NEUROTOXIC EFFECTS: Ineffective on axonal conduction and on membrane potentials.

ANIMALS: Phrenic nerve-diaphragm preparation from Long-Evans rats.

PREPARATION AND DOSE or HISTORY OF PATIENT: Various doses in vitro.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, chemistry

COMPOUND: Colchicine
000064868

REFERENCE: Daniels, M.P.
J. Cell Biol. 58: 463-470, 1973.

OBSERVED NEUROTOXIC EFFECTS: Reversible inhibition of neurite elongation and reversible neurite retraction was seen within 6 hr. Assembly of the microtubules was interrupted and disassembly started. Neurite outgrowth involves assembly.

ANIMALS: In vitro cultures of chick dorsal-root ganglia

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.05 mcg/ml

ROUTE AND SITE: In medium

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Up to 62 hr

EXAM. TYPE: Biochemistry, histology

COMPOUND: Colchicine
000064868

REFERENCE: Wisniewski, H. and Terry, R.D.
Lab. Invest. 17:577-587, 1967.

OBSERVED NEUROTOXIC EFFECTS: After 2 mg died in 2 hr in status epilepticus; others mild paresis by 6 hr quadriparesis by 1 d, died or were killed within 6 d. Large neurons of brainstem and cord altered structurally, and axons distended.

ANIMALS: 15 rabbits, M and F, 3-4 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.01-2.0 mg in 0.1 ml H_2O (one dose)

ROUTE AND SITE: Injection into cisterna magna

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial to 6 d

EXAM. TYPE: Behavior, histology

COMPOUND: Copper (II) chloride
001344678

REFERENCE: Borchard, U. and Schneider, K.U.
Arch. Toxicol. 33:17-30, 1974.

OBSERVED NEUROTOXIC EFFECTS: Amplitude of b-wave of ERG decreased reversibly at Cu 6×10^{-6} m/liter and irreversibly above that, during 30 min of testing. Complexing agents suggested that intoxication might be caused by blocking of enzymes containing sulfhydryl groups.

ANIMALS: Frog retina in vitro

PREPARATION AND DOSE
or HISTORY OF PATIENT: $3\text{-}60 \times 10^{-6}$ m/liter of medium

ROUTE AND SITE: Incubation

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: About 1 hr.

EXAM. TYPE: Electrophysiology (ERG)

! ! 126<

COMPOUND: Copper ion (+2)

REFERENCE: Prakash, N.J., Fontana, J. and Henkin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: At concentrations over 0.01 mM, Cu^{++} completely inhibited (Na^{+} + K^{+}) ATPase. Inhibition involved blockage of norepinephrine and choline uptake.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Cu^{++} chloride added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

COMPOUND: Copper II sulphate
007758987

REFERENCE: Howell, J. McC., Blakemore, W.F., Gopinath, C., Hall, G.A. and Parker, J.H.
Acta Neuropath. 29:9-24, 1974.

OBSERVED NEUROTOXIC EFFECTS: Central Nervous System examined: astrocytic changes, vacuoles in white-matter, swollen astrocytes accumulated glycogen, mitrochondria and endoplasmic reticulum. Authors conclude brain changes in chronic copper poisoning may arise as result of altered glial transport mechanisms.

ANIMALS: Sheep: 39 (Clun Forest x Sussex) and 3 Welsh halfbred, 6-12 mo. old.

PREPARATION AND DOSE or HISTORY OF PATIENT: Av. 7 ppm copper in feed. 29 sheep given 0.5% aqueous soln of copper sulphate daily: 22 at rate of 20 mg/kg, 7 at rate of 30 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 13 sheep untreated

DURATION OF EXPERIMENT: Serial sacr to 37 wk. 9 sacr before, 11 sacr during and 9 died after hemolysis.

EXAM. TYPE: Blood chemistry, histology.

COMPOUND: Copper(II) sulfate pentahydrate (1:1:5)
07758998

REFERENCE: Morgan, K.T.
Res. Vet. Sci. 15: 88-95, 1973.

OBSERVED NEUROTOXIC EFFECTS: The treatment caused a spongy transformation of the white matter. Vacuoles were seen in the myelin and lamellae split, but neurones and glia were not involved and there was no extracellular edema.

ANIMALS: Lambs, 6 mo total 8

PREPARATION AND DOSE or HISTORY OF PATIENT: Diet had 5 ppm of copper; 5 lambs drenched with 1 g compound/d 5 d/wk, 11 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: 3 untreated

DURATION OF EXPERIMENT: 11 wk

EXAM. TYPE: Histology

1274

COMPOUND: Cortisol
000050237

REFERENCE: Heuser, G., Ling, G.M. and Buchwald, H.A.
Arch. Neurol. 13:195-203, 1965.

OBSERVED NEUROTOXIC EFFECTS: Compound produced neither sedation nor seizures in these monkeys.

ANIMALS: Monkeys, Squirrel, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Varying doses, exact amts not given, however comparable to doses of 5-200 mg/kg of other steroid sodium succinate salts.

ROUTE AND SITE: I.V. or I.P.

CONTROL INFORMATION: Sham inj as well as saline and sodium bicarbonate soln were used as controls. Control inj did not produce sedative or convulsion effects.

DURATION OF EXPERIMENT: Up to approx. 30 min/test

EXAM. TYPE: Electrophysiology, behavior

128

COMPOUND: Cortisol, 21-acetate

REFERENCE: Cotterrell, M., Balazs, R. and Johnson, A.L.
J. Neurochem. 19:2151-2167, 1972.

OBSERVED NEUROTOXIC EFFECTS: By 35 d body wt reduced by 50%, brain wt by 30% of norms; 20% fewer cells in cerebrum, 30% in cerebellum; cell size not affected as judged by DNA; cell destruction not affected. Thus growth retardation in terms of new cell divisions was inferred.

ANIMALS: Rats, Porton, M, newborn

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.125-0.4 mg/rat/d, various periods; most rats got 0.2 mg/d for 4 d.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline treated controls

DURATION OF EXPERIMENT: Serial sacr to 35 d.

EXAM. TYPE: Biochemistry.

COMPOUND: Cottonseed oil

REFERENCE: Boyd, E.M. and Boulanger, M.A.
Tox. Appl. Pharm. 14:432-438, 1969.

OBSERVED NEUROTOXIC EFFECTS: The clinical signs included: listlessness, epistaxis, ataxia, and anorexia. Autopsy showed congestion of the brain associated with generalized capillary-venous congestion.

ANIMALS: (1) 20 Rats: Wistar, young, M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-110 mg/kg for 4 d, cumulative amounts of 200-440 ml/kg.

ROUTE AND SITE: I.G.

CONTROL INFORMATION: 66 control rats

DURATION OF EXPERIMENT: 5 d.

EXAM. TYPE: Behavior, autopsy, histopathological

COMPOUND: Coumarin, 3-chloro-7-hydroxy-4-methyl-, bis(2-chloroethyl) phosphate (Haloxon)

REFERENCE: Malone, J.C.
Res. Vet. Sci. 5: 17-31, 1964.

OBSERVED NEUROTOXIC EFFECTS: At high doses, haloxon produced hindleg ataxia in sheep and in poultry. Histological examination revealed axonal degeneration. There was no apparent relationship of the effects with cholinesterase.

ANIMALS: Mice, M, 20-25 g
Rats, S-D, F, 110-150 g
Guinea-pigs, F, 400-600 g
Rats, S-D, weanling, M & F
Cats, adult, no details
Dogs, adult, no details
Monkeys, adult, no details
Hens, 18 mo, 16 groups of 10
Sheep, lambs 1-8 mo, ewes & wethers 1 ; ewes over 4 yr, rams 1-5 yr

PREPARATION AND DOSE or HISTORY OF PATIENT: Many formulations and doses, from LD_{50} down.

ROUTE AND SITE: Oral, in diet; I.P.; dermal.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, biochemistry, histology

129<

COMPOUND: Coumarin,3-Chloro-7-hydroxy-4-methyl,O-ester with O,O-diethyl phosphorothioate
000056724

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 100 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

130

COMPOUND: Coumarin, 7-hydroxy-4-methyl-, bis(2-chloropropyl)phosphate

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Mans, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: O-Cresol, 4,6-dinitro- (DNOC)

000534521

REFERENCE: Burkatskaya, E.N.
Hygiene and Sanitation 30: 197-201, 1965. (Russ.) (Translated)

OBSERVED NEUROTOXIC EFFECTS: Cats (2 of 4) exhibited twitching, tremor, dyspnea and ataxia, with a blood DNOC level of 6-15 mg%; DNOC gradually disappeared from the blood in 6-8 days.
Humans (indoors): changes in central and autonomic nervous systems (sic); (outdoors): only slight changes

ANIMALS: Cats.
Humans (exposed industrially)

PREPARATION AND DOSE or HISTORY OF PATIENT: Cats: 4 exposed to dust containing 0.036-0.06 mg/liter
Humans: exposed to av. 0.9mcg/liter in breathing zone indoors; 0.7 in agriculture

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

COMPOUND: Crotonic acid,3-hydroxy-,alpha-methylbenzylester, dimethyl phosphate, (E)-
007700176

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 200 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Cyanic acid

REFERENCE: Papayannopoulou, T., Stamatoyannopoulos, G., Giblett, E.R. and Anderson, J.
Life Sci. 12(2):127-133, 1973.

OBSERVED NEUROTOXIC EFFECTS: In vitro electrophoretic changes in 25 enzymes. In vivo changes in 10 of these enzymes in 5 tissues including brain homogenates, dose-related; in LD_{50} survivors no changes detected. Changes reversible. Interpreted by authors to show tissue protein carbamylation independent of effects on blood.

ANIMALS: In vitro tissues from "animals";
C_3H mice, aged 12-14 wk, 4 groups total 42 mice.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 80 mg/kg, 12 doses in 3 wk; 100 mg/kg, 5 doses in 1 wk; 22 mg/kg, 17 doses in 3 wk; 250 mg/kg, one dose of the sodium salt (equal to LD_{50}), survivors used.

In vitro: 0.05 M cyanate added to medium incubating blood.

ROUTE AND SITE: I.P. or I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 20-24 hr after last injection.

EXAM. TYPE: Biochemical

132

COMPOUND: Cyanide

000057125

REFERENCE: Bass, N.H.
Neurology 18:167-177, 1968.

OBSERVED NEUROTOXIC EFFECTS: Myelin lesions in somatosensory cortex and subcortical white-matter. At 5 hr after 1 dose white-matter DNA lower by 29%, residue protein up by 28%, cortex gangliosides down by 27%. At 30 d chronic-treated rats had no cortical lesions but white-matter demyelination with 28% gain in residue protein, and losses of DNA (37%) and cerebrosides (65%).

ANIMALS: (1) 30 Rats, COBS, M, adult 300 g.
(2) 10 Rats, COBS, M, adult 300 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Chronic: 8 mg/kg/d stepped up during 25 d in survivor
(2) Acute: 2 mg/rat/10 min for 3 doses.

ROUTE AND SITE: S.C., abdominal wall

CONTROL INFORMATION: 10 rats untreated

DURATION OF EXPERIMENT: 30 d

EXAM. TYPE: Chemistry, Histology

COMPOUND: Cyanide

000057125

REFERENCE: Hirano, A., Leving, S. and Zimmerman, H.M.
J. Neuropath. Exp. Neurol. 27(2):234-245, 1968.

OBSERVED NEUROTOXIC EFFECTS: Corpus callosum and callosal radiation (the only tissues reported on) had distortions of remyelination shown at 4 mo. after intoxication. Observations, not fully reported, imply that demyelination had occurred on intoxication.

ANIMALS: Rats, young albino.

PREPARATION AND DOSE or HISTORY OF PATIENT: Deep intoxication for 30 min (ref. Leving, S. and Stypulkowski, W. Arch. Path. 67:306 (1959)).

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 wk to 6 mo. after intoxication, serial sacr.

EXAM. TYPE: Electronmicroscopy

COMPOUND: Cyanide

000057125

REFERENCE: Van Houten, W.H. and Friede, R.L.
Exp. Neurology 4:402-412, 1961.

OBSERVED NEUROTOXIC EFFECTS: Increase of oxidative enzymatic activity in white matter; increase of enzyme activity in neuroglia cell perikarya-astrocytes. Edema, anoxia.

ANIMALS: 45 Rats, Albino, 200-300 mg.

PREPARATION AND DOSE or HISTORY OF PATIENT: Inhalation of air bubbled through 10% soln of potassium cyanide in a 1 gallon jar until animal became unconscious and remained so for 20 mins. Few given additional exposures at 24 hr intervals.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Animals killed 24 hrs or more after last exposure

EXAM. TYPE: Histochemical.

COMPOUND: 1,3,5-Cycloheptatriene

000544252

REFERENCE: Brown, V.K.H., Ferrigan, L.W. and Stevenson, D.E.
Ann. Occup. Hyg. 10:123-126, 1967.

OBSERVED NEUROTOXIC EFFECTS: Clonic convulsions preceded death. (LD_{50} dosages).

ANIMALS: Rats, Hooded Lister, 4 M and 4 F/group, 150-250 g Mice, CF No. 1, 4 M and 4 F, 21-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: Oral 57 mg/kg percutaneous 442-884 mg/kg
Mice: Oral 171 mg/kg

ROUTE AND SITE: Gavage, topical (dorso-lumbar skin)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Death in 24 hr, usually in minutes

EXAM. TYPE: Behavior, histopathological

134

COMPOUND: Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma-isomer

000058899

REFERENCE: Czegledi-Janko, G. and Avar, P.
Br. J. Indust. Med. 27: 283-286, 1970.

OBSERVED NEUROTOXIC EFFECTS: EEG and clinical findings increased with blood concentration over 0.02 ppm.

ANIMALS: 37 men, working in a fertilizer factory.

PREPARATION AND DOSE or HISTORY OF PATIENT: Final product contained 1.5% lindane; no other toxic agent, but 22 subjects had previous exposure to aldrin, 3 acute histories (convulsions), another 3 EEG disorders. Lindane not measured, exposure lasted 0.5-2 yr. Blood levels 0.002-0.340 ppm.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: Blood levels in 20 of general population 0.003-0.017 ppm.

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Blood lindane, EEG, clinical.

COMPOUND: Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma isomer (Lindane)

000058899

REFERENCE: St. Omer, V.
J. Neurochem. 18: 365-374, 1971.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, starting in some cases during injection. Intensity and other signs were directly related to increases of brain ammonia. Toxicity ranking: lindane > dieldrin > heptachlor > DDT. Brain glutamine increases resulting from conversion of ammonia to glutamine were related to the toxicity ranking, suggesting that the 4 compounds produced convulsions by one mechanism involving interference with the production and/or utilization of ammonia.

ANIMALS: Rats, adult F, Wistar, 250-300 g, surgically prepared.
Cockerels, White Leghorn or Barred Plymouth Rock, 12 wk, 1.4-1.6 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: mg/kg -- lindane 11.5, DDT 50, dieldrin 6, heptachlor 13
Cockerels: mg/kg -- lindane 6.3, DDT 30, dieldrin 6, heptachlo
The compounds stated to be structurally unrelated.

ROUTE AND SITE: Intra-arterial (carotid) at 1 ml/min

CONTROL INFORMATION: Vehicle o...

DURATION OF EXPERIMENT: Up to 60 min, in controls 7 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: 5H-Cyclooct(b)indole, 5-(3-(dimethylamino)propyl)-6,7,8,9,10,11-hexahydro-
005560725

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. (Berl.) 29: 237-249, 1974.

OBSERVED NEUROTOXIC EFFECTS: Significant ultrastructural alterations of nerve cells, both in spinal cord and in cerebellar cortex.

ANIMALS: Rats, Wistar, M, young adult

PREPARATION AND DOSE
or HISTORY OF PATIENT: 125 mg/kg bw, 5d/wk in water, 0.5 ml/100 g bw, for 5 wk.

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: Force-fed pure water.

DURATION OF EXPERIMENT: 5 wk

EXAM. TYPE: Histology

135

COMPOUND: Cyclopentanecarboxylic acid, 1-amino

000052528

REFERENCE: Rose, R.B., Noll, C.I., Rose, W.C.J., Hadkarni, M.V., Morrison, B.H., Jr., and Bond, H.W.
J. Med. Pharm. Chem. 3:1-23, 1961.

OBSERVED NEUROTOXIC EFFECTS: Dogs: Slight demyelination of cerebellum.
Mice: Slight demyelination of central nervous system.
Nerve effects not mentioned for other species.

ANIMALS: Dogs, rats, mice, cats, monkeys, humans

PREPARATION AND DOSE
or HISTORY OF PATIENT: Dogs: 31.6 mg/kg/d for 30 d (lower doses no effect; LD_{50} one dose was 300 mg/kg).
Mice: 200-1259 mg/kg.

ROUTE AND SITE: Dogs: Oral (capsule) Mice: Gavage

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT:

EXAM. TYPE: Clinical, autopsy

136

COMPOUND: Cyclopentane carboxylic acid, 1-phenyl-, 2-(diethylamino)ethyl ester, hydrochloride
000125859

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 25 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Cyclopropylamine, 2-phenyl-, sulfate trans- (+,-)-, (2:1)

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 4 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Cysteine, L-

REFERENCE: Olney, J.W. and Ho., O.
Nature 227:609-610, 1970.

OBSERVED NEUROTOXIC EFFECTS: Necrosis of hypothalamic neurons in mice given glutamate, aspartate, or cysteine, dose-related; zero damage from other compounds

ANIMALS: 75 Mice, Swiss Webster, age 10 d.

PREPARATION AND DOSE or HISTORY OF PATIENT: One of 10 amino acids and various other compounds, 2.5 or 10% in water, 0.25-2 g/kg.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Intubated, no treatment, 10 mice

DURATION OF EXPERIMENT: 5 hr.

EXAM. TYPE: Histology

1372

COMPOUND: Cysteine, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

138

COMPOUND: Cysteine, N-acetyl-, L-

000616911

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE
or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Decaborane (14)

017702419

REFERENCE: Feinsilver, L., Lawson, L.H., Yevich, P.P. and Jacobson, K.H.
U.S. Army CWL Report CWLR 2367, 1960.

OBSERVED NEUROTOXIC EFFECTS: LC_{50} under conditions were:
Rats - 46ppm; mice - 12ppm. Signs included ataxia, depression, prostration, tremors, clonic convulsions, interpreted as "marked effects upon" the central nervous system.

ANIMALS: Rats, ages 8-10 wk, M
Mice, 8-10 wk, F
Dogs, beagle, M.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposed to vapors of compounds in LC_{50} study, 2-4 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Observation to 7 d after exposure

EXAM. TYPE: Behavior, pathology

COMPOUND: Decaborane, ethyl

REFERENCE: Feinsilver, L., Lawson, L.H., Yevich, P.P. and Jacobson, K.H.
U.S. Army CWL Report CWLR 2367, 1960.

OBSERVED NEUROTOXIC EFFECTS: LC_{50} under conditions were:
Rats - 23ppm; mice - 6ppm; dogs - approximately 6ppm. Signs included ataxia, depression, prostration, tremors, clonic convulsions, interpreted as "marked effects upon" the central nervous system.

ANIMALS: Rats, ages 8-10 wk, M
Mice, 8-10 wk, F
Dogs, beagle, M.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposed to vapors of compounds in LC_{50} study, 2-4 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Observation to 7 d after exposure

EXAM. TYPE: Behavior, pathology

139

COMPOUND: 1,4-Diazabicyclo(2.2.2.)octane

REFERENCE: Goldberg, M.E. and Johnson, H.E.
Tox. Appl. Pharm. 4:522-545, 1962.

OBSERVED NEUROTOXIC EFFECTS: Treatment apparently stimulated sympathetic ganglia.

ANIMALS: Rats, CFE, M, 5-6 wk old, 90-120 g, 5 rats/grp or 6/grp (inhalation)
Rabbits, NZ white, 2.5-3.5 kg, M, 4 rabbits/grp, and isolated ileum.
Mice, white, F, 20-28 g.
41 mongrel dogs (8.5-12.5 kg) M and F. 10 cats, F, 2.2-3.8 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various schedules

ROUTE AND SITE: Topical, shaved skin (rabbits); inhalation (rats, mice); intra-arterial (carotid) (dogs, cats) and I.V. femoral (dogs, cats)

CONTROL INFORMATION: Varied

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Physiology, biochemistry

140A

COMPOUND: 5H-Dibenz(b,f)azepine, 3-chloro-5-(3-(dimethylaminopropyl)-10, 11-dihydro-

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. (Berl.) 29: 237-249, 1974.

OBSERVED NEUROTOXIC EFFECTS: Very mild changes in the fine structure of neuronal lysosomes, in cord and cerebellar cortex.

ANIMALS: Rats, Wistar, M, young adult

PREPARATION AND DOSE or HISTORY OF PATIENT: 150 mg/kg bw, 5d/wk, in water 0.5 ml/100 g bw for 4 wk.

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: Controls force-fed pure water

DURATION OF EXPERIMENT: 4 wk.

EXAM. TYPE: Histology

COMPOUND: 5H-Dibenz(b,f) azepine, 5-(3-(dimethylamino)propyl)-10,11-dihydro-

000050497

REFERENCE: Pearlman, C. and Becker, M.
Psychopharmacologia 42:63-66, 1975.

OBSERVED NEUROTOXIC EFFECTS: Cooperative behavior training and performance prevented when compound administered a few minutes after feeding session, no effects if given 3 hr afterwards. Authors concluded mechanism was prevention of REM sleep during this time.

ANIMALS: Rats, Long-Evans, F, 3 mo. age.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg/kg on alternate days a few minutes after session or after 3 hrs of rest.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 6 controls: undisturbed sleep, 6 had saline inj followed by normal sleep.

DURATION OF EXPERIMENT: Approx. 10 d

EXAM. TYPE: Behavior

COMPOUND: 5H-Dibenz(b,f) azepine, 5-(3-(dimethylamino)propyl)-10,11-dihydro-, monohydrochloride
000113520

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 6 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

141

COMPOUND: 5H-Dibenzo-(a,d)cycloheptene-delta (sup 5), gamma-propylamine 1-chloro-10,11-dihydro-N,N-dimethyl-

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. (Berl.) 29: 237-249, 1974.

OBSERVED NEUROTOXIC EFFECTS: Significant ultrastructural alterations of nerve cells, both in spinal cord and in cerebellar cortex.

ANIMALS: Rats, Wistar, M, young adult

PREPARATION AND DOSE or HISTORY OF PATIENT: 120 mg/kg bw, 5d/wk in water, 0.5 ml/100 g bw for 10 wk

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: Controls force-fed pure water

DURATION OF EXPERIMENT: 10 wk

EXAM. TYPE: Histology

142

COMPOUND: 5H-Dibenzo(a,d) cycloheptene-delta (Sup 5), gamma-propylamine, 10,11-dihydro-N,N-dimethyl-
000050486

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. (Berl.)29: 237-249, 1974

OBSERVED NEUROTOXIC EFFECTS: Administration for 10wk did not induce alterations in the nerve cells of spinal cord and cerebellar cortex cells examined.

ANIMALS: Rats, Wistar, M, young adult.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 150 mg/kg bw, 5d/wk in water, 0.5 ml/100 g bw, for 8 wk.

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: Controls force-fed pure water.

DURATION OF EXPERIMENT: 8 wk.

EXAM. TYPE: Histology

COMPOUND: 5H-Dibenzo(a,d) cycloheptene-delta (sup5), gamma-propylamine, 10,11-dihydro N,N-dimethyl-, hydrochloride
000549188

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} 4 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: 5H-Dibenzo(a,d)cyclohepten-5-one, 10,11-dihydro-,o-(2-(dimethyl amino)ethyl)oxime

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. 29: 237-249, 1974.

OBSERVED NEUROTOXIC EFFECTS: Administration for 10 wk did not induce alterations in the nerve cells of spinal cord and cerebellar cortex cells examined.

ANIMALS: Rats, Wistar, M, young adult.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 150 mg/kg bw, 5d/wk, in water 0.5 ml/100g bw for 8 wk

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: Controls force fed pure water

DURATION OF EXPERIMENT: 8 wk

EXAM. TYPE: Histology

143

COMPOUND: Dibenzo-p-dioxin,2,3,7,8-tetrachloro
001746016

REFERENCE: Oliver, R.M.
Br. J Indust, Med. 32:49-53, 1975.

OBSERVED NEUROTOXIC EFFECTS: Personality disorders, emotional instability, loss of hearing, sense of smell or taste. Headaches and blurred vision. Neuropathy recovered over approx. 6 mo.

ANIMALS: 3 Humans: M, age 45, 33, 35 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Scientists in the same lab, extent of exposure unknown.

ROUTE AND SITE: Unknown

CONTROL INFORMATION: 3 other scientists in same lab with no known exposure to dioxin.

DURATION OF EXPERIMENT: 3 yr.

EXAM. TYPE: Clinical, biochemical

144

COMPOUND: 6H-Dibenzo(b,d)pyran-1-01,3-(1'2'-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl- (Dimethylheptylpyran)

REFERENCE: Karler, R., Cely, W. and Turkanis, S.A.
Res. Comm. Chem. Path. Pharm. 7(2):353-358, 1974.

OBSERVED NEUROTOXIC EFFECTS: Bar-walk test gave decreasing order of toxicity as dimethylheptylpyran, Δ^9-tetrahydrocannabinol, cannabidiol; anticonvulsant and "toxic" actions concluded to be separable.

ANIMALS: Mice, ICR, 4-5 wk old

PREPARATION AND DOSE or HISTORY OF PATIENT: 3-20 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Own controls

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-7-alpha, 11-dihydroxy-6,6,9-trimethyl-3-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. This compound was approx. seven times more potent by intracerebral admin. than by I.V.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-7-beta,11-dihydroxy-6,6,9-trimethyl-3-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. This compound was approx. seven times more potent by intracerebral admin. than by I.V.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

145A

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-8,11-dihydroxy-6,6,9-trimethyl-3-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. This compound was significantly more potent by intracerebral admin. than by I.V.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

146

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a, 7,10,10a-tetrahydro-11-hydroxy-6,6,9-trimethyl-3-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. This compound was approx. seven times more potent by intracerebral admin. than by I.V.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. Immobility was more pronounced with the Δ^8 THC compounds. Equipotent by either method of admin, faster onset of activity after intracerebral. Activity after I.V. may be due to conversion to 11-hydroxy metabolite.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-

REFERENCE: McCaughran, J.A., Jr., Corcoran, M.E. and Wada, J.A.
Pharm. Biochem. Behav. 2: 227-233, 1974.

OBSERVED NEUROTOXIC EFFECTS: The rats exhibited flaccid muscle, ataxia, catalepsy, hyperreactivity, and loss of righting. These symptoms were dose-related from 0 (1 mg/kg) to 100% (9 mg/kg). A TD_{50} of 4.3 mg/kg was determined. Protection against metrazol induced seizures was provided by far higher doses.

ANIMALS: Rats, hooded, M, 300-480 g, total over 200 in groups of 4

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1-9 mg/kg, one dose (toxicity)
15-200 mg/kg (protection against induced seizures)

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior

1972

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,[6 aR-trans]-

1972083

REFERENCE: Carlini, E.A., Karniol, I.G., Renault, P.F. and Schuster, C.R.
Br. J. Pharmac. 50: 299-309, 1974.

OBSERVED NEUROTOXIC EFFECTS: The compound disrupted time production tasks, increased pulse rate and provoked psychic reactions in humans. The different animals responded similarly.

ANIMALS: Rabbits, albino, adult M, 2.5-3.5 kg
Mice, albino, M, 3 mo, 25-30 g
Rats, no details
Human: 11 physicians and 22 medical students, all M, 18-42 yr, 51-80 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Rabbits: continuous infusions
Rats: 0-40 mg/kg
Mice: 0-80 mg/kg
Humans: 1-20 mg/man

ROUTE AND SITE: Rabbits: I.V.; rats: ns; mice: I.P.; humans: inhalation.

CONTROL INFORMATION: Zero treatment, placebo

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior

148

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6 aR-trans)-

1972083

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, was compared to other cannabinoids. Similar neurological and behavioral responses were found for all provided that high concentrations were given. Behavioral pattern was characterized by irritability, decrease in spontaneous activity, reduced sensorimotor responses. The potency of the compounds varied depending on structure and route of administration. Measurable behavioral alterations after intracerebral 0.05 mg. Compound is approximately equipotent by either method of administration, however, faster onset of activity after intracerebral.

ANIMALS: Mice. Also in vitro study of metabolism.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.05 mg, 0.2 mg or 0.5 mg.
Relative potency of Δ THC to related compounds given in table.
In vitro: 1.0 mg labeled/g tissue for 1 hr in 0.1M potassium phosphate buffer.

ROUTE AND SITE: I.V., or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, biochemistry

COMPOUND: 6H-Dibenzo(b,d) pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6 aR-trans)-

1972083

REFERENCE: Fried, P.A. and Husband, C.A. Life Sci. 12(1):289-295, 1973.

OBSERVED NEUROTOXIC EFFECTS: Visual cliff test. No differences in depth perception in treated vs control groups. Acute group took significantly longer than other groups to perform the tests.

ANIMALS: 43 Rats, hooded, M, Aged 2 mo, 6 grps of 7-8 rats

PREPARATION AND DOSE or HISTORY OF PATIENT: Chronic: 0.5 or 4 mg/kg in propylene glycol, 1/2 d for 44 d prior to testing.
Acute: 0.5 or 4 mg/kg once, preceded by 21 inj 0.5 cc propylene glycol 1/2 d.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 1 group vehicle only, 1 group sham inj.

DURATION OF EXPERIMENT: 44 d plus testing time.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d) pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6 aR-trans)-

1972083

REFERENCE: Fujimori, M., Trusty, D.M. and Himwich, H.E.
Life Sci. 12(1):553-563, 1973.

OBSERVED NEUROTOXIC EFFECTS: Simultaneous EEG changes, hypotension, slow EKG, all dose-dependent. Authors suggest mechanism of action may be different from that of other psychotomimetrics.

ANIMALS: 46 Rabbits, white, 3.1-3.7 kg, tracheotomized, 10-12/grp

PREPARATION AND DOSE or HISTORY OF PATIENT: 4 different doses: 0.1, 0.5, 1.0 and 2.0 mg/kg as 1 mg/ml in soln of 10% propylene glycol.

ROUTE AND SITE: I.V. rate 1 ml/min.

CONTROL INFORMATION: Control measurements taken prior to testing of compound.

DURATION OF EXPERIMENT: Serial sacr 0-90 min after dose.

EXAM. TYPE: Electrophysiological

149<

COMPOUND: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-

REFERENCE: Hockman, C.H., Perrin, R.G. and Kalant, H.
Science 172:968-970, 1971.

OBSERVED NEUROTOXIC EFFECTS: Doses at all levels produced disruption of both behavior and electroencephalogram.

ANIMALS: 6 Cats, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5, 1 and 4 mg/kg to each cat in successive trials, 4-7 d intervals.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Self-controls

DURATION OF EXPERIMENT: 60-min sessions

EXAM. TYPE: Electrophysiology, behavior

150

COMPOUND: 6H-Dibenzo(b,d) pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6 aR-trans)-

1972083

REFERENCE: Karler, R., Cely, W. and Turkanis, S.A.
Res. Comm. Chem. Path. Pharm. 7(2):353-358, 1974.

OBSERVED NEUROTOXIC EFFECTS: Bar-walk test gave decreasing order of toxicity as dimethylheptylpyran, the above compound, cannabidiol; anticonvulsant and "toxic" actions concluded to be separable.

ANIMALS: Mice, ICR, 4-5 wk old

PREPARATION AND DOSE or HISTORY OF PATIENT: 40-130 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Own controls

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

COMPOUND: 6H-Dibenzo(b,d) pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6 aR-trans)-

1972083

REFERENCE: McCaughran, J.A., Jr., Corcoran, M.E. and Wada, J.A.
Pharm. Biochem. Behav. 2: 227-233, 1974.

OBSERVED NEUROTOXIC EFFECTS: The rats exhibited flaccid muscles, ataxia, catalepsy, hyperreactivity, and loss of righting. These symptoms were dose-related from 0 (1 mg/kg) to 100% (9 mg/kg). A TD_{50} of 3.4 mg/kg was determined. Protection against metrazol induced seizures was provided by far higher doses.

ANIMALS: Rats, hooded, M, 300-480 g, total over 200 in groups of 4

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-9 mg/kg, one dose (toxicity)
15-200 mg/kg (protection against induced seizures)

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior

COMPOUND: Dibenzylamine, N-(2-chloroethyl)-

000051503

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 50 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

151A

COMPOUND: Diethylamine, 2,2'-dichloro-N-methyl-

000051752

REFERENCE: McDonald, T.P. and Asano, M.
Am. J. Path. 38:695-702, 1964.

OBSERVED NEUROTOXIC EFFECTS: Severe, dose-related, neuronal shrinkage with later focal necrosis, peak on d 6-8. Most affected: neocortex, pyriform cortex, hippocampus, cerebellum, medulla oblongata. Signs: inactivity, incoordination, irritability, convulsions, lacrimation.

ANIMALS: Mice, RF, F aged 10 wk, 21-26 g, total 189 used in an acute toxicity study.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.05-0.4 mg/mouse in 0.9% NaCl at pH 4.2-4.6.

ROUTE AND SITE: I.V., dorsal caudal vein

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 1-28 d

EXAM. TYPE: Histology, behavior

152

COMPOUND: 6,7-Dihydrodipyrido[1,2-a:2',1'-c] pyrazidiinium dibromide

REFERENCE: Clark, D.G. and Hurst, E.W.
Brit. J. Industr. Med. 27: 51-55, 1970.

OBSERVED NEUROTOXIC EFFECTS: Large doses (4 or 5 times LD_{50}) produced signs indicative of an action on the central nervous system: lethargy, labored respiration, muscular twitching, generalized convulsions.

ANIMALS: Rats, Alderly Park (albino), 180-200 g

PREPARATION AND DOSE or HISTORY OF PATIENT: Compound given as dichloride or dibromide, 99% pure, LD_{50}: 10-11 mg/kg

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 13 d

EXAM. TYPE: Clinical

COMPOUND: 1,4:5,8-Dimethanonaphthalene, acetoxy-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-, exo-

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity of giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared Housefiles, NAIDM strain

PREPARATION AND DOSE or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7.8,8a-octahydro-,endo,endo-
000072208

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity of giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic. DDT with other compounds produced effects not seen with any compound alone.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared
Housefiles, NAIDM strain

PREPARATION AND DOSE
or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

153A

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7,epoxy-1,4,4a,5,6,7,8,8a-octahydro, endo, exo- (Dieldrin)
000060571

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity of giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic. DDT with other compounds produced effects not seen with any compound alone.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared
Housefiles, NAIDM strain

PREPARATION AND DOSE
or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

154

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7,epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo- (Dieldrin)

000060571

REFERENCE: St. Omer, V.
J. Neurochem. 18: 365-374, 1971.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, starting in some cases during injection. Intensity and other signs were directly related to increases of brain ammonia. Toxicity ranking: lindane > dieldrin > heptachlor > DDT. Brain glutamine increases resulting from conversion of ammonia to glutamine were related to the toxicity ranking, suggesting that the 4 compounds produced convulsions by one mechanism involving interference with the production and/or utilization of ammonia.

ANIMALS: Rats, adult F, Wistar, 250-300 g, surgically prepared.
Cockerels, White Leghorn or Barred Plymouth Rock, 12 wk, 1.4-1.6 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: mg/kg -- lindane 11.5, DDT 50, dieldrin 6, heptachlor 13.
Cockerels: mg/kg -- lindane 6.3, DDT 30, dieldrin 6, heptachlor 6.3.
The compounds stated to be structurally unrelated.

ROUTE AND SITE: Intra-arterial (carotid) at 1 ml/min

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: Up to 60 min, in controls 7 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7,epoxy-1,4,4a, 5,6,7,8,8a-octahydro, endo, exo- (Dieldrin)

000060571

REFERENCE: Schaffer, C.H. and Sun, Y.P.
J. Econ. Entomol. 60: 1580-1583, 1967.

OBSERVED NEUROTOXIC EFFECTS: No evidence found that binding within the fly central nervous system is a factor in resistance; no metabolism of dieldrin in central nervous system tissues was detected in resistant or susceptible flies. The authors concluded that resistance might be due to insensitivity at the receptor site.

ANIMALS: Houseflies (Musca domestica)

PREPARATION AND DOSE or HISTORY OF PATIENT: In most cases, 0.02 mcg/fly; 25 mcg/fly to resistant flies

ROUTE AND SITE: Injection or infusion

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Up to 24 hr

EXAM. TYPE: Biochemistry, behavior

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-, endo, endo-
000309002

REFERENCE: Avar, P., Czegledi-Janko, G.
Brit. J. Industr. Med. 27:279-282, 1970.

OBSERVED NEUROTOXIC EFFECTS: Three had epileptiform fits.

ANIMALS: 15, humans from plant manufacturing aldrin and lindane, M.

PREPARATION AND DOSE
or HISTORY OF PATIENT: .02, .039, .014, .006 ppm HEOD in whole blood.

ROUTE AND SITE: ns.

CONTROL INFORMATION: 12 Humans

DURATION OF EXPERIMENT: 2 yrs.

EXAM. TYPE: EEG, biochemistry, neurology

155<

COMPOUND: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-, endo, endo-
000309002

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity of giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic. DDT with other compounds produced effects not seen with any compound alone.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared
Housefiles, NAIDM strain

PREPARATION AND DOSE
or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

156

COMPOUND: 4-Dimethylamino-3,5 xylyl methylcarbamate, 22.3% emulsifiable concentrate

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 4.4 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 3 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Distannoxane, hexabutyl-

000056359

REFERENCE: Robinson, I.M.
Fd. Cosmet. Toxicol. 7: 45-52, 1969

OBSERVED NEUROTOXIC EFFECTS: Treatment lowered brain epinephrine, norepinephrine and serotonin for 48 hours.

ANIMALS: Rats, Osborne-Mendel, F, 190-220 g, 18/group

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg in corn oil

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Equivalent corn oil

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Disulfide, bis(diethylthiocarbamoyl)

0000977778

REFERENCE: Gardner-Thorpe, C. and Benjamin, S.
J. Neurol. Neurosurg, Paychiat. 34:253-259, 1971.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy and optic neuritis.

ANIMALS: Human: 7 case-reports

PREPARATION AND DOSE
or HISTORY OF PATIENT: 250-1500 mg/d for alcoholism, long term.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Follow-up to 2 yr after discontinuing drug

EXAM. TYPE: Clinical chemistry, behavior, nerve-conduction tests

157

COMPOUND: Ephedrine HCl

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} 4 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

158

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Brown, I.R. and Liew, C.C.
Science 188:1122-1123, 1975.

OBSERVED NEUROTOXIC EFFECTS: LSD stimulated acetylation of specific histones in cerebral hemispheres and midbrain 30 min after injection.

ANIMALS: Rabbits, young NZ White, M, 1 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 and 100 mcg/kg in 0.1 ml saline.

ROUTE AND SITE: I.V., ear vein

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: 15 and 30 min

EXAM. TYPE: Biochemistry

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-meth

000050373

REFERENCE: Diaz, J-L. and Huttunen, M.O.
Science 174:62-63, 1971.

OBSERVED NEUROTOXIC EFFECTS: Chronic oral intake raised synthesis and turnover of 5-HT by 25-30%, and levels of 5-HT (13%) and tryptophan (18%). No "grossly" evident behavioral changes in treated rats.

ANIMALS: Rats, S-D, M, 150-160 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mcg/kg/d in 1.0 ml water for 1 mo. The dose was increased daily according to weight gain.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls treated water only.

DURATION OF EXPERIMENT: 1 mo.

EXAM. TYPE: Biochemistry

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-diehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Farrow, J.T. and Van Vunakis, H.
Biochem. Pharmacol. 22:1103-1113, 1973.

OBSERVED NEUROTOXIC EFFECTS: Synaptosomes of cortical grey-matter contained low concentrations of high- and medium- affinity binding-sites for LSD. Synaptic membranes had 2.2 times more high-affinity sites/mg protein but only 1.8 times more medium-affinity sites than synaptosomes. These sites are not found elsewhere in the brain. Binding inhibited by chlorpromazine or any of 10 other hallucinogens; enhanced by cAMP or prostaglandin E_1.

ANIMALS: Rat cerebral cortex fractions in vitro.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Myelin, synaptosomes, mitochondria obtained by centrimgation and verifeid by electronmicroscopy. Binding of ^{3}H-LSD studied.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemical

159>

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Idanpaan-Heikkila, J.E. and Schoolar, J.C.
Science 164:1295-1297, 1969.

OBSERVED NEUROTOXIC EFFECTS: Brain uptake higher than blood concentration. Part of dose (2.5% early in pregnancy, 0.5% late) passed into the fetuses in 5 min, over 70% being unmetabolized LSD. For 30 min LSD in cortex higher than in white-matter. Related behavior started at 3-4 min and lasted 40-60 min.

ANIMALS: Mice, Yale Swiss, 4 M and 6 F pregnant

PREPARATION AND DOSE
or HISTORY OF PATIENT: 19.8 and 9.9 mcg/g of labeled compound.

ROUTE AND SITE: I.V., tailvein

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Serial sacr 5 min to 24 hr.

EXAM. TYPE: Autoradiography

160<

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Peters, D.A.
Biochem. Pharmacol. 23:231-237, 1974.

OBSERVED NEUROTOXIC EFFECTS: Brainstem: norepinephine and tyrosine hydroxylase lower after 20 mcg/kg/d for 14 d, more so after 100 mcg/kg/d. Mixed results with serotonin and 5-hydroxyindoleacetic acid.

ANIMALS: Rats, S-D, M, 160-180 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 500 mcg/kg in saline 2 ml/kg. One dose, or 5 x 100 mcg/kg half-hourly for 5 doses (acute). 500 mcg/kg/d (chronic). Sacrifice 24 hr after last dose. Chronic rats also given lower daily amounts (from 20 mcg) ns. under Methods.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline only, all studies.

DURATION OF EXPERIMENT: 14 d (chronic)

EXAM. TYPE: Biochemical

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >10 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl

000050373

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced excitement, abnormal postures, arousal EEGs, then depression.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.025-0.1 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

161

COMPOUND: Ergoline-8-beta-Carboxylic acid, 9,10-didehydro-6-methyl-,morpholide

REFERENCE: Gogerty, J.H. and Dille, J.M.
J. Pharm. Exp. Ther. 120: 340-348, 1957.

OBSERVED NEUROTOXIC EFFECTS: The compound induced behavior changes like those from LSD, the equivalent dose being one-third more than LSD and the duration of effects half as long.

ANIMALS: Mice, albino, 25 g
Cats
Rabbits
Rats, F
Human: 2 volunteers

PREPARATION AND DOSE
or HISTORY OF PATIENT: Various schedules and doses

ROUTE AND SITE: I.V. (mice, cats, rabbits); S.C. (rats); oral (humans)

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, clinical

1627

COMPOUND: Ergotamine, dihydro-, monomethanesulfonate

001381028

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >20 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: D-Erythro-D-galacto-octo pyranoside, methyl 6,8-dideoxy-6-(1-methyl-4-propyl-2-pyrrolidine carboxamido)-1-thio-

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: (1 and 2) Depressed neuromuscular transmission at doses of 25 and 50 mg/kg. (3) Immediate ataxia, higher doses were lethal.

ANIMALS: (1 and 2) 6 Rabbits
(3) 3 Chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 25 mg/kg followed by 50 mg/kg, in saline.
(2) 50 mg/kg during each of four stimulation frequencies in a latin-square design.
(3) 200 mg/kg or 300-500 mg/kg.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, behavior

COMPOUND: Ethanamine

000075047

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-

REFERENCE: Chang, L.W., Dudley, A.W., Jr., Lee, Y.K. and Katz, J.
Exp. Neurol. 45: 209-219, 1974.

OBSERVED NEUROTOXIC EFFECTS: Superior parasagittal cerebral cortex showed collapses of neuronal rough endoplasmic reticulum, dilated Golgi complex, and some vacuoles in cytoplasm. After higher dose, effects more severe: loss of mitochondrial membranes, coagulative necrosis of cortical neurons, and edematous glial cells.

ANIMALS: Rats, young M and F

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 5 rats: 10 ppm 8 hr/d, 5d/wk for 8 wk.
(2) 5 rats: 500 ppm 8 hr/d, 5d/wk for 4 wk.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: 6 control rats

DURATION OF EXPERIMENT: (1) 8 wk, (2) 4 wk

EXAM. TYPE: Histology

164

COMPOUND: Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-

REFERENCE: Chang, L.W., Dudley, A.W., Jr., Katz, J. and Martin, A.H. Teratology 9:A-15, 1974. (Abstract)

OBSERVED NEUROTOXIC EFFECTS: No gross fetal anomalies. Brain ultrastructure of newborn focal weakness/disruption of cortical neurons, vacuolation, myelin anomalies, abnormal synapses.

ANIMALS: Rats, S-D, pregnant F

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 ppm, 40 hr/wk thru pregnancy.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Gestation

EXAM. TYPE: Histology

COMPOUND: Ethane, 1,1'-oxybis-

000060297

REFERENCE: Denst, J. Neurology 3: 239-249, 1959.

OBSERVED NEUROTOXIC EFFECTS: Coma from 8 hours to 35 days. Cerebral lesions characterized by: anemic infarction, loss of Purkinje cells, and severe gliosis of the molecular layer of the cerebellum; neuronal degeneration and focal necrosis of cortex degeneration of basal nuclei; necrosis of cerebral white matter with giant-cell granulomas. This damage was not attributed to anoxemia or circulatory stagnation.

ANIMALS: Human: 3 cases (M, 8; M, 72; F, 33)

PREPARATION AND DOSE or HISTORY OF PATIENT: Anesthesia by open-drip or closed system

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 35 d

EXAM. TYPE: Clinical; autopsy

COMPOUND: Ethane, 1,1'-oxybis-(ether)

000060297

REFERENCE: Owens, G.
Neurology 8: 827-831, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions were recorded by EEG in dogs subjected to hyperthermia and ether anesthesia, probably due to fat embolisms. Prior heparinization protected the animals.

ANIMALS: Dogs, 2 groups of 10

PREPARATION AND DOSE
or HISTORY OF PATIENT: Closed gas system, dose ns

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Up to 2 wk

EXAM. TYPE: Clinical, biochemistry, histology

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: Dale, W.E., Gaines, T.B. and Hayes, W.J., Jr.
Tox. Appl. Pharm. 4: 89-106, 1962.

OBSERVED NEUROTOXIC EFFECTS: Signs correlated with increases of DDT concentration in brain induced by starvation; this concentration was not parallel with concentrations of metabolites DDE (plasma metabolite) and DDA (urinary metabolite). Tremors developed during the 12th week.

ANIMALS: Rats, Sherman, 22-28 d old weanlings, M & F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 200 ppm DDT in diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated rats

DURATION OF EXPERIMENT: Up to 140 d

EXAM. TYPE: Behavior, biochemistry

165

166

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-

000050293

REFERENCE: Dvorchik, B.H. and Maren, T.H.
Comp. Gen. Pharm. 5: 37-49, 1974.

OBSERVED NEUROTOXIC EFFECTS: The compound was taken up by all tissues and stored mainly in the liver and muscle with no significant storage in red cells nor excretion. Metabolism was slow (after 17 d 95% of liver store was intact). The brain level at autopsy after receiving the LD_{50} suggested that the brain was more sensitive to the compound than that of mammals.

ANIMALS: Dogfish, M, 1-3 kg (Squalus acanthias)

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-20 mg/kg, or 60 mcg/kg of labeled compound

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Sham injections

DURATION OF EXPERIMENT: 1 hr to 15 d (serial), or longer (1 mo)

EXAM. TYPE: Biochemistry

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: Eaton, J.L. and Sternburg, J.G.
J. Econ. Entomol. 60: 1699-1703, 1967.

OBSERVED NEUROTOXIC EFFECTS: The frequency of DDT-induced trains in the abdominal central nervous system was not directly related to the DDT content of the central nervous system. More trains appeared after topical application than after injection, although less DDT was found in the abdominal central nervous system. Injection into the 6th abdominal ganglion produced dose-related trains indicating that high afferent (sensory) activity was needed. Therefore, the synaptic block following DDT was secondary to some more direct action of DDT or a metabolite.

ANIMALS: American cockroach (Periplaneta americana), adult M.

PREPARATION AND DOSE or HISTORY OF PATIENT: (a) 120 mcg/cockroach
(b) 1 mcg/cockroach

ROUTE AND SITE: (a) Topical, on both cerci; (b) Injected into the 6th abdominal ganglion

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Probably 24 hr

EXAM. TYPE: Electrophysiology, biochemistry

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: Peters, D.A.V., Hrdina, P.D., Singhal, R.L. and Ling, G.M.
J. Neurochem. 19:1131-1136, 1972.

OBSERVED NEUROTOXIC EFFECTS: A single dose raised the brainstem 5-hydroxyindoleacetic acid but not 5-hydroxytryptamine. Pretreatment with Pargyline allowed 5-hydroxytryptamine to increase. Administration of DL-p-chlorophenylalanine with DDT blocked the rise of 5-hydroxyindoleacetic acid and neuropathy signs (pyrexia, tremors, convulsions) from DDT. DL-6-fluorotryptophan (serotonin inhibitor) blocked the rise of 5-hydroxyindoleacetic acid and pyrexia but not tremors and convulsions. The authors infer that 5-hydroxytryptamine turnover is connected with pyrexia.

ANIMALS: Rats, Wistar, M, 190-220 g, at least 4/grp.

PREPARATION AND DOSE or HISTORY OF PATIENT: 600 mg/kg in corn oil with/without other compounds.

ROUTE AND SITE: Oral; other compounds given I.P.

CONTROL INFORMATION: One group, vehicle

DURATION OF EXPERIMENT: Serial to 5 hr.

EXAM. TYPE: Biochemistry

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity of giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic. DDT with other compounds produced effects not seen with any compound alone.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared
Housefiles, NAIDM strain

PREPARATION AND DOSE or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

167>

168

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: St. Omer, V.
J. Neurochem. 18: 365-374, 1971.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, starting in some cases during injection. Intensity and other signs were directly related to increases of brain ammonia. Toxicity ranking: lindane > dieldrin > heptachlor > DDT. Brain glutamine increases resulting from conversion of ammonia to glutamine were related to the toxicity ranking, suggesting that the 4 compounds produced convulsions by one mechanism involving interference with the production and/or utilization of ammonia.

ANIMALS: Rats, adult F, Wistar, 250-300 g, surgically prepared.
Cockerels, White Leghorn or Barred Plymouth Rock, 12 wk, 1.4-1.6 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: mg/kg -- lindane 11.5, DDT 50, dieldrin 6, heptachlor 13.
Cockerels: mg/kg -- lindane 6.3, DDT 30, dieldrin 6, heptachlor 6.3.
The compounds stated to be structurally unrelated.

ROUTE AND SITE: Intra-arterial (carotid) at 1 ml/min

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: Up to 60 min, in controls 7 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)- (DDT)

000050293

REFERENCE: Shankland, D.L.
Tox. Appl. Pharm. 6:197-213, 1964.

OBSERVED NEUROTOXIC EFFECTS: Symptoms in hindlimbs if spinal reflexes functioned, then excised tibial nerves responded to electrostimulation. Without reflexes, neither symptoms arose, nor did excised nerves respond. Course of DDT-tremors similar to that in the American cockroach.

ANIMALS: Rats, Purdue-Wistar (sic), M and F, 150-400 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-300 mg/kg in oil, 100 mg/ml

ROUTE AND SITE: Gavage or instillation into throat

CONTROL INFORMATION: Untrtd rats

DURATION OF EXPERIMENT: ns., apparently up to about 1 wk

EXAM. TYPE: Electrophysiology, behavior

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-

000050293

REFERENCE: Wooley, D.E. and Barron, B.A.
Tox. Appl. Pharm. 12: 440-454, 1968.

OBSERVED NEUROTOXIC EFFECTS: Hyperexcitability and tremors. Mild clonic convulsions occurred only rarely, but seen in rats which died. Spontaneous electric activity changed before onset of tremors (10 areas measured), most in cerebellum.

ANIMALS: 22 Rats, S-D, F, 200-250 g, surgically prepared.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50 and 100 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

169>

COMPOUND: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-

000050293

REFERENCE: Woolley, D.E. and Runnells, A.L.
Tox. Appl. Pharm. 11:389-395, 1967.

OBSERVED NEUROTOXIC EFFECTS: High peak concentration of compound in central nervous system grey-matter by 6-12 hr, slower uptake and lower concentration in myelinated tissues, e.g. brainstem and cord. Hyperirritability and tremor more intense at 6-12 hr than at 24 hr, corresponding with peak concentrations in neocortex and cerebellum. Fine tremor thought related to brain peak, coarse tremor to cord peak.

ANIMALS: Rats, S-D, F, 200-250 g, total 24.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg after 24-hr fast.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: 4 rats untrtd

DURATION OF EXPERIMENT: 6, 12, 24 hr

EXAM. TYPE: Biochemistry

170

COMPOUND: Ethanol, 2-butylamino

000111751

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols and choline analogs, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ethanol, 2-(p-chlorophenyl)-1-(p-(2-(diethylamino)ethoxy)phenyl)-1-p-tolyl-

000078411

REFERENCE: Suzuki, K., Zagoren, J.C., Chen, S.M. and Suzuki, K.
Acta Neuropath. 29:141-156, 1974.

OBSERVED NEUROTOXIC EFFECTS: Intracytoplasmic osmiophilic inclusions throughout central nervous system in all treated rats, dose-related, followed by degeneration especially of oligodendroglia, and demyelination. Large accumulations of $\Delta^{7,24}$-cholestadiene-3β-ol and (less) of desmosterol. Authors state that the former produces identical lesions and attribute them (see also under 20, 25-diazacholesterol) to the presence of a double bond at the 7-position.

ANIMALS: Rats, Wistar, M and F, newborn

PREPARATION AND DOSE or HISTORY OF PATIENT: 250 mg/kg/d in olive oil, from d 5 of age.

ROUTE AND SITE: Oral or I.P.

CONTROL INFORMATION: Olive oil only, or (biochemistry) untreated

DURATION OF EXPERIMENT: Serial, 3-9 d

EXAM. TYPE: Histology, biochemistry

COMPOUND: Ethanol, 2-(dibutylamino)-

000102818

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values. When given i.p., compound reduced brain cholinesterase.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ethanol, 2-(diethylamino)-

000100378

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

172

COMPOUND: Ethanol, 2-dimethylamino-

000108010

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values. When given i.p., compound reduced brain cholinesterase.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ethanol, 2-(ethylamino)-

000110736

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the I.P. LD_{50} values. When given i.p., compound reduced brain cholinesterase.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ethanol, 2-methoxy-

000109864

REFERENCE: Goldberg, M.E., Haun, C. and Smyth, H.F.
Tox. Appl. Pharm. 4:148-164, 1962.

OBSERVED NEUROTOXIC EFFECTS: Specific inhibition of conditioned avoidance - escape behavior without motor imbalance. Given i.p., barbiturate hypnosis was potentiated, same if inhaled; pretreatment with LSD antagonized this effect.

ANIMALS: Rats: DW or CFE, F, 130 g
Mice: White, F, 22 g

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5-2 mg/kg
(2) 125-32,000 ppm in air

ROUTE AND SITE: (1) I.P. (2) Inhalation

CONTROL INFORMATION: Untreated groups

DURATION OF EXPERIMENT: Various schedules

EXAM. TYPE: Behavior

173

COMPOUND: Ethanol, 2-methoxy-

000109864

REFERENCE: Greenburg, L., Mayers, M.R., Goldwater, L.J. Burke, W.J. and Moskowitz, S.
J. Ind. Hyg. Toxicol. 20:134-147, 1938.

OBSERVED NEUROTOXIC EFFECTS: Abnormal reflexes, tremor, mental retardation, lethargy; abnormal blood picutre. Compound only the probable cause of the neuropathy.

ANIMALS: Humans 19 M 16-26 yr (av. 20)

PREPARATION AND DOSE or HISTORY OF PATIENT: Industrial exposure 25-76 ppm, occasionally more; other compounds in mix EtOH, MeOH, ethylacetate, petroleum naptha. Exposures of 1-3 mo.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 yr of follow-up

EXAM. TYPE: Hematology, Behavior

174

COMPOUND: Ethanol, 2-(methylamino)-

00019831

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other amino-ethanols, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the compounds molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Ether, chloromethyl methyl

000107302

REFERENCE: Laskin, S., Drew, R.T., Cappiello, V., Kuschner, M. and Nelson, N.
Arch. Env. Hlth. 30:70-72, 1975.

OBSERVED NEUROTOXIC EFFECTS: One rat developed esthioneuroepithelioma of olfactory epithelium after exposure; one rat developed undifferentiated pituitary tumor considered "coincidental."

ANIMALS: 74 Rats, 90 hamsters

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 ppm, 6 hr/d, 5 d/wk, 565 exposures in 852 d.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: 74 Rats, 88 hamsters

DURATION OF EXPERIMENT: 128 wk after 1st exposure

EXAM. TYPE: Carcinogenesis bioassay

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Ahtee, L. and Svartstrom-Fraser, M.
Acta Pharmacol. Toxicol. 36:289-298, 1975.

OBSERVED NEUROTOXIC EFFECTS: Rigidity, convulsions. Rapid disappearance and low levels of noradrenaline in brain.

ANIMALS: Rats, M, S-D, 250-300 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 8-11 g/kg/d, 7-10 d, then withdrawal.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Untreated controls

DURATION OF EXPERIMENT: Maximum 11d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Bauer-Moffett, C. and Altman, J.
Exp. Neurol. 48:378-382, 1975.

OBSERVED NEUROTOXIC EFFECTS: Histology on 2 rats/litter. Dry and wet wt of cerebellum reduced by 26%, of rest of brain by about 14%. Reduction of Purkinje cells averaged 27.4%. Bodyweights, livers, lungs all found normal; thiamine 10 mcg/d did not relieve damage.

ANIMALS: Rats, Purdue-Wistar, cross-fostered, 8/litter.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 3.5-4.0% in air, inhaled for 2 x 90 min/d for 3-20 d. Cardiac blood after 2nd exposure averaged 268 mg EtOH/ 100 ml; all rats remained conscious. Experiment started at day 3 of age.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Air only

DURATION OF EXPERIMENT: 20 d

EXAM. TYPE: Histology

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Blum, K., Wallace, J.E. and Geller, I.
Science 176:292-294, 1972.

OBSERVED NEUROTOXIC EFFECTS: Glycine or serine enhanced ethanol-induced sleeptime; authors inferred interaction in the central nervous system.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mmoles/100 g and/or 0.45-0.9 mmole/100 g of glycine.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline

DURATION OF EXPERIMENT: Up to 140 min.

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Davis, V.E. and Walsh, M.J.
Science 167:1005-1007, 1970.

OBSERVED NEUROTOXIC EFFECTS: Ethanol indirectly augmented formation of tetrahydropapaveroline, a morphine-like compound.

ANIMALS: Rat brainstem homogenates in vitro.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Incubation mixture with dopamine and added EtOH 100 mM, or acetaldehyde 0.5-2 mM.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: 30 min

EXAM. TYPE: Biochemistry

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Decker, J.B., Wells, C.E. and McDowell, F.
Neurology 9: 361-366, 1959.

OBSERVED NEUROTOXIC EFFECTS: Leg function of the patients suggested cerebellar dysfunction, which responded to diet and supplements. The authors concluded that ethanol rather than diet deficits had been the cause.

ANIMALS: Human: 10 patients aged 33-68, all M

PREPARATION AND DOSE
or HISTORY OF PATIENT: History of prolonged alcoholism with poor diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

1774

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Goldberg, M.E., Haun, C. and Smyth, H.F.
Tox. Appl. Pharm. 4:148-164, 1962.

OBSERVED NEUROTOXIC EFFECTS: Treatment did not produce inhibition of conditioned avoidance-escape behavior without motor imbalance separately from ataxia.

ANIMALS: Rats: DW or CFE, F, 130 g
Mice: White, F, 22 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2,000-32,000 ppm in air.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Untreated groups

DURATION OF EXPERIMENT: Various schedules.

EXAM. TYPE: Behavior

178

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Israel, M.A. and Kuriyama, K.
Life Sci. 10(2):591-599, 1971.

OBSERVED NEUROTOXIC EFFECTS: Mitochondrial ATPase rose after acute and chronic ethanol. The increase was mainly Mg^{++}-dependent, ouabain-insensitive, and not DNP-activated. No effect on ATPase in synaptosomes or microsomes.

ANIMALS: Mice, Siss albino, M, 25-28 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Acute: 4 g/kg as 20% w/v in saline.
Chronic: 6% w/v of diet.

ROUTE AND SITE: Acute: I.P. Chronic: Oral

CONTROL INFORMATION: Sucrose instead of compound.

DURATION OF EXPERIMENT: 2 wk.

EXAM. TYPE: Biochemistry

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Jarlstedt, J. and Hamberger, A.
J. Neurochem. 19:2299-2306, 1972.

OBSERVED NEUROTOXIC EFFECTS: Ethanol diminshed incorporation of leucine into glial but not neuronal proteins.

ANIMALS: Rats, S-D, M, 100-110 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1. 3.2 g/kg, preceded by 15 hr fast.
2. 0.1-5% in medium to brain cortex slices.

ROUTE AND SITE: I.P.; in vitro

CONTROL INFORMATION: Saline treated controls

DURATION OF EXPERIMENT: 3 hr.

EXAM. TYPE: Biochemistry

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Kuriyama, K. and Israel, M.A.
Biochem. Pharmacol. 22:2919-2922, 1973.

OBSERVED NEUROTOXIC EFFECTS: Adenyl cyclase activity in homogenates of cerebral cortex declined after 10 min incubation of controls but not of ethanol groups; no change of phosphodiesterase activity. No effect of in vitro. additions of ethanol; nevertheless cAMP content increased significantly, all groups.

ANIMALS: Mouse, Swiss albino, F, 25-30 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 6% in liquid diet, av. intake 7-9 ml/d, dose of ethanol 16-21 g/kg. Acute study: 4 g/kg.

ROUTE AND SITE: Oral. Acute study: I.P.

CONTROL INFORMATION: Control group treated isocaloric sucrose diet.

DURATION OF EXPERIMENT: 3 wk.

EXAM. TYPE: Biochemical

1796

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Kuriyama, K., Sze, P.Y. and Rauscher, G.E.
Life Sci. 10(2):181-189, 1971.

OBSERVED NEUROTOXIC EFFECTS: Protein synthesis by brain ribosomes was inhibited acutely (3 hr) and increased chronically (7-14 d) in vivo. Not related to blood ethanol levels, or to observed central nervous system depression.

ANIMALS: Mice, Swiss ablino, M, 25-28 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Acute: 4 g/kg as 20% w/v in saline, 1 dose.
Chronic: liquid died 6% ethanol.

ROUTE AND SITE: Acute: I.P. Chronic: Oral

CONTROL INFORMATION: Control group sucrose treated.

DURATION OF EXPERIMENT: Serial sacr to 14 d

EXAM. TYPE: Biochemistry

180>

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Melville, K., Jordon, G., Douglas, D.
Toxicology and Applied Pharmacology 9:363-375, 1966.

OBSERVED NEUROTOXIC EFFECTS: Ataxia with depression; maximal effects occurred during 1st hr. Synergistic action with glutethimide increased central nervous system depression and produced surgical anesthesia.

ANIMALS: Mongrel dogs, 7.0-12.0 kg, M and F.

PREPARATION AND DOSE or HISTORY OF PATIENT: 50% soln of EtOH in water. Dose of 1 ml/kg hourly, 3 or 5 times.

ROUTE AND SITE: Stomach tube

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: More than 1 wk.

EXAM. TYPE: Behavior

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Novak, D.J. and Victor, M.
Arch. Neurol. 30: 273-284, 1974.

OBSERVED NEUROTOXIC EFFECTS: Non-inflammatory degeneration of myelinated nerve fibers affecting peripheral nerves (legs more than arms). Denervation atrophy. Primary degeneration of the vagus nerves, lesions acute and extended throughout all portions of the nerve.

ANIMALS: 4 human alcoholics.

PREPARATION AND DOSE or HISTORY OF PATIENT: Alcoholic neuropathy with hoarseness and weakness of the voice, dysphagia, and derangements of the autonomic nervous functions.

ROUTE AND SITE: Oral.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: "Many years"

EXAM. TYPE: Histology

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Roach, M.K., Davis, D.L., Pennington, W. and Nordyke, E.
Life Sci. 12(1):433-441, 1973.

OBSERVED NEUROTOXIC EFFECTS: Ethanol inhibited active active transport of probable neurotransmitters of the central nervous system by synaptosomes. Authors conclude that alcohol interacts with membrane lipids of synaptosome.

ANIMALS: Rats, S-D, M, 200-250 g, brains removed and homogenates incubated in vitro.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Ethanol added as 25% soln, at start of preincubation period. Ethanol conc 5-30 mg/ml. Incubated in vitro with labeled norepinephrine, GABA and glutamate.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Control: incubation in medium with no alcohol.

DURATION OF EXPERIMENT: Laboratory procedure.

EXAM. TYPE: Biochemistry.

181<

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Skillicorn, S.A.
Neurology 5:524-534, 1955.

OBSERVED NEUROTOXIC EFFECTS: Ataxia of legs; no nystagmus; pneumoencephalograms suggested diffuse degenerative disease of the cerebrum as well as cerebellar atrophy of a presenile type.

ANIMALS: Human: 6 cases, 39-55 at onset

PREPARATION AND DOSE
or HISTORY OF PATIENT: History of prolonged chronic alcoholism and gait disorder lasting 1-15 yr

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 mo

EXAM. TYPE: Clinical, neurological

182

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Sutton, I. and Simmonds, M.A.
Biochem. Pharmacol. 22:1685-1692, 1973.

OBSERVED NEUROTOXIC EFFECTS: Endogenous γ-aminobutyric acid (GABA) no change after acute ethanol but increased 48% after chronic treatment. Exogenous GABA disappeared at same rate throughout, The enzyme GAD increased after acute ethanol treatment, and the enzyme GABA-T increased after chronic ethanol.

ANIMALS: Rats, Wistar, M., 160-200 g (acute), 130 g (chronic)

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: 4g/kg as 20% soln in saline, preceded by 24 hr fast and followed 30 min by admin. of labeled GABA.
(2) Chronic: 14% in water as only drink for 3 wk, followed by 24 hr fast and admin labeled GABA.

ROUTE AND SITE: Acute: I.P., Chronic: Oral

CONTROL INFORMATION: Acute: saline treated only, Chronic: water treated only.
All: GABA or no GABA.

DURATION OF EXPERIMENT: 3 wk.

EXAM. TYPE: Biochemical

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Tytell, M. and Myers, R.D.
Biochem. Pharmacol. 22:361-372, 1973.

OBSERVED NEUROTOXIC EFFECTS: Acute (see below) rats converted more 5-hydroxytryptamine to 5-hydroxyindoleacetic acid than chronic or controls in caudate nucleus; chronics no different from controls; no differences in production of 5-hydroxytrytophol. In this, "some parts" of central nervous system differ from peripheral nervous system, according to the authors.

ANIMALS: Rats, adult Royal Victoria hooded (sex ns.), 3 per group (acute, chronic, control)

PREPARATION AND DOSE
or HISTORY OF PATIENT: All rats prepared surgically for brain perfusion, 3 sites, with labeled serotonin.
Acute: 6 g/kg EtOH in 20% v/v solution intragastric
Chronic: Sole drink 8% v/v EtOH plus 2% malt extract.
Control: Water ad lib, no treatment.

ROUTE AND SITE: Oral or intragastric

CONTROL INFORMATION: 3 Rats, as stated above.

DURATION OF EXPERIMENT: 130-147 d

EXAM. TYPE: Biochemical

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Veloso, D., Passonneau, J.V. and Veech, R.L.
J. Neurochem. 19:2679-2686, 1972.

OBSERVED NEUROTOXIC EFFECTS: (1) Rats lost their righting reflex within 6-7 min. after injection, general anesthesia within 8 min. Rises of brain glucose, G6P and citrate, no change in arterial pCO_2.
(2) General anesthesia, rises of glucose, G6P, glycogen, arterial pCO_2, falls of lactate, pyruvate, α-oxoglutarate, malate, glutamate, aspartate. Interpreted as effects on nerve cell membrane, contrasted with liver where ADH is "primary target."

ANIMALS: Rats, S-D, M. 390-400 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: Rats starved for 72 hr prior to treatment.
1. Acute: 3.5 ml of 7M ethanol in 0.15M NaCl.
2. Chronic: 3 ml at 13 and 5 hr and 1 ml at 3 and 1 hr. prior to brain removal. 7 M ethanol in 0.15 m NaCl.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls treated with 0.15M NaCl.

DURATION OF EXPERIMENT: Acute: 8 min; Chronic: 13 hr.

EXAM. TYPE: Behavior, biochemistry

183A

COMPOUND: Ethyl alcohol

000064175

REFERENCE: Walsh, J.C. and McLeod, J.G.
J. Neurol. Sci. 10:457-469, 1970.

OBSERVED NEUROTOXIC EFFECTS: Slow sensory and motor conduction; sural nerves (myelinated fibers) axonal or Wallerian degeneration and regeneration.

ANIMALS: 11 Humans with alcoholic peripheral neuropathy, ages 41-73 yr (av 58 yr).

PREPARATION AND DOSE
or HISTORY OF PATIENT: Studied within 3 wk of admission to hospital.

ROUTE AND SITE:

CONTROL INFORMATION: 20 control subjects aged 38-73 yr (av 54).

DURATION OF EXPERIMENT:

EXAM. TYPE: Electrophysiology, histology (biopsy)

184>

COMPOUND: Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B. J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic ß-chloroethylamines but not when (a) OH or bromine replaced the ß chlorine, (b) a ß-phenyl group replaced one of the ß hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary ß-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-ß-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g: also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

COMPOUND: Ethylamine, 2-chloro-N,N-dipropyl-

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B. J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic ß-chloroethylamines but not when (a) OH or bromine replaced the ß chlorine, (b) a ß-phenyl group replaced one of the ß hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary ß-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-ß-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

COMPOUND: Ethylamine, 2-chloro-N-ethyl-N-methyl-, hydrochloride

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B. J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic β-chloroethylamines but not when (a) OH or bromine replaced the β chlorine, (b) a β-phenyl group replaced one of the β hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary β-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-β-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

1857

COMPOUND: Ethylamine, N-chloro-methyl-N-propyl-2-, hydrochloride

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B. J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic β-chloroethylamines but not when (a) OH or bromine replaced the β chlorine, (b) a β-phenyl group replaced one of the β hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary β-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-β-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

! ! 186>

COMPOUND: Ethylamine, N,N-dimethyl-2-(o-methyl-alpha-phenylbenzyl-oxy)-

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Ethylamine, N,N-dimethyl-2-((o-methyl-alpha-phenylbenzyl) oxy)-, hydrochloride
000341695

REFERENCE: Gill, D.G. and Sowerby, H.A.
Practitioner 214: 542-544, 1975.

OBSERVED NEUROTOXIC EFFECTS: Epileptiform seizures, status epilepticus. Plasma compound level was 12.3 and 5.1 mcg/ml. Both cases recovered. The authors reviewed fatal cases with lower plasma levels.

ANIMALS: Human: 2 cases, F, 23 mo 12 kg; F, 52 mo 17.1 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: In both cases, compound was prescribed for iatrogenic illness and was swallowed accidentally by children; 300 mg, unknown amount.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 3 d, 4 d

EXAM. TYPE: Clinical, biochemistry

COMPOUND: Ethylamine, 2-(diphenylmethoxy)-N,N-dimethyl-
000058731

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Ethylene, tetrachloro-
000127184

REFERENCE: Haerer, A.F. and Udelman, H.D.
Am. J. Psychiat. 121: 78-79, 1964.

OBSERVED NEUROTOXIC EFFECTS: The subject developed amnesia within 2 hours, suffering confusion, irritation, hallucinations, distorted color-vision, and speech difficulty. All symptoms cleared within 3 hours of the dose with no sequelae.

ANIMALS: Human: one isolated case, M, 21

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 ml, one dose, prescribed as anthelmintic; history noncontributory.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 3 hr with follow-up

EXAM. TYPE: Clinical

186

COMPOUND: Ethylene, trichloro-

000070916

REFERENCE: Buxton, P.H. and Hayward, M.
J. Neurol. Neurosurg, Psychiat. 30:511-518, 1967.

OBSERVED NEUROTOXIC EFFECTS: Exposure-related: after 10 min, headache and nausea for 48 hr; after 30 min, vomiting and numbness for 15 d; after 2.5 hr, dizziness progressing to facial diplegia by d 9, residual visual and trigeminal motor signs present after 2.5 yr, 4 hr, facial diplegia by d 6, tracheostomy needed by d 12, continual vomiting and emaciation, died after 51 d. Damage most severe in brainstem and Vth-nerves; changes in cerebral and cerebellar cortexes attributed to secondary hypoxemia. Peripheral nervous system and cord, where examined, showed little damage.

ANIMALS: Human: 4 case-reports including 1 autopsy.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Industrial accident, exposure for 10 min. to 4 hr. while cleaning tanks without respirators.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Other operators wearing fresh-air respirators had no effects.

DURATION OF EXPERIMENT: 51 d, 2 1/2 yr.

EXAM. TYPE: History, clinical observation, autopsy

COMPOUND: Ethylene, trichloro-

0000 9016

REFERENCE: Fe.dman, R.G., Mayer, R.M. and Taub, A.
Neurology 20:599-606, 1970.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, trigeminal sensory loss, authors infer demyelination.

ANIMALS: Human: one case

PREPARATION AND DOSE
or HISTORY OF PATIENT: Industrial exposure to vapor for 5 min and indirect exposure via closed-circuit gasmask for 1.5 hr.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Follow-up period, more than one month.

EXAM. TYPE: Behavior, electrophysiology, clinical tests

COMPOUND: Ethyl (beta-hydroxy ethyl)trimethylammonium hydroxide

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols and choline analogs, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-amino-ethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

189

COMPOUND: Ethyl (m-hydroxyphenyl) dimethylammonium chloride

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: Produced consistent partial antagonism, the effects of lincomycin were never completely reversed by edrophonium.

ANIMALS: 4 Rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: 10-100 mcg/kg administered at peak of the neuromuscular blockade from lincomycin (50 mg/kg).

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

1905

COMPOUND: Folic acid

000059303

REFERENCE: Baxter, M.G., Miller, A.A. and Webster, R.A.
Br. J. Pharmac. 49: 350P-351P, 1973 (abstract of proceedings).

OBSERVED NEUROTOXIC EFFECTS: Convulsive doses (ED_{50}) reported by three routes and compared with those of six other compounds (leptazol, picrotoxin, strychnine, bicuculline, glutamate, ouabain). Folic acid produces a flexor-extensor convulsion pattern.

ANIMALS: Mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 17-1024 mcg/mouse

ROUTE AND SITE: I.V. and intracerebroventricular, also oral.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior

COMPOUND: Folic acid, sodium salt

REFERENCE: Hill, R.G. and Miller, A.A.
Br. J. Pharmac. 50: 425-427, 1974.

OBSERVED NEUROTOXIC EFFECTS: The compound reduced presynaptic inhibition produced by peripheral stimulation, and is a known convulsant. The authors infer that both folic acid and picrotoxin act by the same mechanism.

ANIMALS: 6 piebald Lister rats, adult, surgically prepared

PREPARATION AND DOSE
or HISTORY OF PATIENT: Concentrations: 0.1-1% w/v (1 to 10 mM)

ROUTE AND SITE: Cannulated onto the surface of the cuneate nucleus

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: About 2 hr per test

EXAM. TYPE: Electrophysiology

COMPOUND: Formaldehyde

000050000

REFERENCE: Kulle, T.J. and Cooper, G.P.
Arch. Env. Hlth. 30:237-243, 1975.

OBSERVED NEUROTOXIC EFFECTS: Examined effects of prolonged exposure. Formaldehyde decreased response to amyl alcohol directly according to concentration; perfusion with air for 1 hr. partly restored response.

ANIMALS: Rats, S-D, M, 250-400 g, surgically prepared for testing of nasopalatine nerve twigs.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5, 1.0, 1.5, or 2.0 ppm for continuously for 1 hr. Repeated tests in many animals, for total exposure of 4 hr.

ROUTE AND SITE: Gas drawn through nasal cavities by vacuum pump.

CONTROL INFORMATION: Pre-exposure control responsiveness determined by test series of amyl alcohol (0.3, 0.7, 1.0, 3.3, 6.7, 10.0 pph) and then repeated after exposure to test compound. Air controls also run.

DURATION OF EXPERIMENT: Several hr.

EXAM. TYPE: Electrophysiology.

191>

COMPOUND: Formanilide, 2'-(3-bromo-2-thienyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

192

COMPOUND: Formanilide, 2'-(3-bromo-4-thienyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Formanilide, 2'(2-bromo-3-thienyl)thio-5'-chloro-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Formanilide, 2'-(3-bromo-2-thienyl)thio-5'-chloro

REFERENCE: Grol, C.J. and Rollema, H.
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ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Formanilide, 2'-(3-bromo-4-thienyl)thio-5'-chloro

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

1933

COMPOUND: Formanilide, 2'-(2-bromo-3-thienyl)thio-5'-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Formanilide, 5'-chloro-2'-(3-thienyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Formanilide, 2'-(3-thienyl)thio-5'-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

195

COMPOUND: Furoyl hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.48 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

196

COMPOUND: Galactose

REFERENCE: Malone, J.I., Wells, H.J. and Segal, S.
Science 174:952-954, 1971.

OBSERVED NEUROTOXIC EFFECTS: Severe hyperosmolar dehydration which, according to authors, could account for toxic changes in brain chemistry.

ANIMALS: Chicks, Rhode Island Red, day-old

PREPARATION AND DOSE or HISTORY OF PATIENT: 10% w/v in drinking water for 2 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Controls water alone

DURATION OF EXPERIMENT: 2 d

EXAM. TYPE: Biochemistry

COMPOUND: D-Galactose

REFERENCE: Blosser, J.C. and Wells, W.W.
J. Neurochem. 19:1539-1547, 1972.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity was produced, and neural lysosomes were studied. Fragility higher than controls. Enzyme studies indicated a role of galactitol as well as of galactose.

ANIMALS: Cockerels, Leghorn, day-old

PREPARATION AND DOSE or HISTORY OF PATIENT: 40% (w/w) in diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION:

DURATION OF EXPERIMENT: Up to 64 hr.

EXAM. TYPE: Biochemistry

COMPOUND: D-Galactose

REFERENCE: Granett, S.E., Kozak, L.P., McIntyre, J.P. abd Wells, W.W. J. Neurochem. 19:1659-1670, 1972.

OBSERVED NEUROTOXIC EFFECTS: Levels of ATP, G6P (down by 9 hr), FDP, 3PG, α-GP, lactate (not down till 18 hr), and glucose and glycogen (later stages; G1P, citrate and cAMP not altered) suggested that compound interfered with brain uptake of glucose.

ANIMALS: Chicks, White Leghorn, M, 1-2 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: 40% D-galactose w/w in place of glucose in diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Glucose treated controls

DURATION OF EXPERIMENT: Up to 50 hr.

EXAM. TYPE: Biochemistry

1974

COMPOUND: Galactosiduronic acid, methyl-, methyl ester, polymer of sulfated sodium salt

REFERENCE: Joseph, A.D.
Br. J. Pharmacol. 17: 533-538, 1961.

OBSERVED NEUROTOXIC EFFECTS: 5-10 mg of mepesulfate produced tremor, salivation, tachypnea, loud calling, seizures, blind charging, and then somnolence within minutes. Complete recovery in 24 hours. 2.5 mg produced few or no such effects.

ANIMALS: Cats, no details, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-10 mg
2.5 mg

ROUTE AND SITE: Cannulated into left lateral ventricle of brain

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Weeks

EXAM. TYPE: Behavior

198

COMPOUND: Gallium Fluoride

REFERENCE: Meige, J.W.
J. Occup. Med. 14: 225-226, 1972.

OBSERVED NEUROTOXIC EFFECTS: Pain, motor weakness of extensor muscles (localized), blood negative for lead and mercury, recovery after 3 mo, neurology attributed to gallium.

ANIMALS: 1 Human, F. 43, research chemist.

PREPARATION AND DOSE or HISTORY OF PATIENT: Lab exposure to fumes from crystals + H_2O.

ROUTE AND SITE: Skin contact, hands and arms (despite use of fume hood), inhalation.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 3 mo.

EXAM. TYPE: Clinical, blood chemistry

COMPOUND: Gasoline

MX8006619

REFERENCE: Saito, K.
Brit. J. Indust. Med. 30:352-358, 1973.

OBSERVED NEUROTOXIC EFFECTS: Evidence of tension and excitement after 6-7 d in rats given lead; after 1-3 d EEG showed decreased δ,θ and α waves for both types of gasoline; cortex showed marked α and θ activity after 6-7 d in lead rats. Lead content and cortical recordings correlated.

ANIMALS: 19 rats, Wistar, M, 330-453 g, aged 7 mo., surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 ml/kg; from leaded gasoline rats received 16.5 mg/kg of tetraethyl lead (LD_{50} 13.2-18 mg/kg); one dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Follow-up for 10 d

EXAM. TYPE: Electrophysiology (EEG)

COMPOUND: beta-D-Glucopyranoside, (methyl-ONN-azoxy)methyl-

014901087

REFERENCE: Hirano, A., Dembitzer, H.M., and Jones, M.
J. Neuropath. Exp. Neurol. 31(1): 113-125, 1972.

OBSERVED NEUROTOXIC EFFECTS: Severe ataxia. Granule cells absent, but postsynaptic Purkinje cell dendritic spines present, surrounded by astrocytic cytoplasm, resembling post-synaptic endings. Membranous thickening apposed dense material in intercellular cleft. Possible development of Purkinje cell dendritic spines, independent of presynaptic ending.

ANIMALS: Mice, Swiss albino, newborn

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 mg/g

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Saline only

DURATION OF EXPERIMENT: 25 d

EXAM. TYPE: Electron microscopy

1996

COMPOUND: beta-D-Glucopyranoside,(methyl-ONN-azoxy)methyl-

014901087

REFERENCE: Jones, M.
Am. J. Path. 62:69, 1971. (Abstract)

OBSERVED NEUROTOXIC EFFECTS: Ataxia, abnormal gait, diminished cerebellum with diminutive granule cells, disarrangement of layers. Clinical signs did not persist in less severe cases. No lesions in cord.

ANIMALS: Mice, Swiss albino

PREPARATION AND DOSE
or HISTORY OF PATIENT: ns.

ROUTE AND SITE: ns.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns. but at least 90 d

EXAM. TYPE: Clinical, histology

002

COMPOUND: beta-D-Glucopyranoside,(methyl-ONN-azoxy)methyl)-

014901087

REFERENCE: Hirono, I. and Shibuya, C.
Nature 216:1311-1312, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, posterior paralysis, many deaths; nerve histology (incomplete at time of writing) negative. In acute study (2) death occurred without neurological signs.

ANIMALS: (1) 60 newborn mice from 11 C57BL/6 F mice.
(2) 58 mice, C57BL/6, aged 2 mo.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 mg/g one dose, in saline.
(2) 0.3/0.5/1 mg/g, one dose in saline.

ROUTE AND SITE: (1) S.C., dorsal (2) Gavage

CONTROL INFORMATION: (1) 21 newborn to 3 dams, saline only (2) ns.

DURATION OF EXPERIMENT: Over 8 mo. follow-up of 34 survivors.

EXAM. TYPE: Behavior, histology

COMPOUND: beta-D-Glucopyranoside, (methyl-ONN-azoxy)methyl)-

014901087

REFERENCE: Hirono, I., Shibuya, C. and Hayashi, K.
Proc. Soc. Exp. Biol. Med. 131:593-599, 1969.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, disturbed gait; necrosis of granular layer of cerebellum in newborn, persisting as developmental defect in mature animals. These in mice and hamsters; rats not affected.

ANIMALS: 18 Golden hamsters, F, their 150 newborn, and 23 mature hamsters
29 rats, Moriyamaso, F, their 276 newborn
3 similar rats, their 21 newborn
72 C57BL/6 mice, F, their 415 newborn; 10 dd mice, their 64 newborn.

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: 0.5 or 1 mg/g one dose at various times.
Hamsters: 0.15-0.6 mg/g one dose at various times.
Rats: 0.5 mg/g or 250 mg/kg, various times.

ROUTE AND SITE: Oral or S.C.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Serial sacr up to 72 hr, some animals to maturity.

EXAM. TYPE: Behavior, histology

COMPOUND: Glue vapors

REFERENCE: Shirabe, T., Tsuda, T., Terao, A. and Araki, S.
J. Neurol. Sci. 21: 101-113, 1974.

OBSERVED NEUROTOXIC EFFECTS: Polyneuropathy after 2.5-3 yr exposure, mainly motor with limb weakness and muscle-wasting, progressing after exposure ceased. Sural nerve extensive axonal degeneration, no regeneration 3 mo. after exposure ceased. Neurogenic atrophy of skeletal muscle. Deep sensation stimuli retarded, superficial sensation stimuli less affected.

ANIMALS: Human: M, 20; M, 19, both painters.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Glue-sniffing for 3 and 2 yr respectively.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Follow-up 3 mo.

EXAM. TYPE: Histology (biopsy), clinical

201>

COMPOUND: Glutaconic acid, 3-hydroxy-, dimethyl ester, dimethyl phosphate

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 9.45 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

202<

COMPOUND: Glutamic acid

REFERENCE: Van Harreveld, A. and Fifkova, E.
Exp. Mol. Path. 15:61-81, 1971.

OBSERVED NEUROTOXIC EFFECTS: Compound damage to cortex distinguished from method-artifacts, dose-related. Edema, destruction and removal of "dark" nerve cells.

ANIMALS: Rats, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative dosage

ROUTE AND SITE: Electrophoretic injection

CONTROL INFORMATION: Microelectrodes filled with Ringer's soln were used as controls.

DURATION OF EXPERIMENT: 1 hr to 15 d.

EXAM. TYPE: Histology

COMPOUND: Glutamic acid

REFERENCE: Zarzecki, P., Blum, P.S., Cordingley, G.E. and Somjen, G.G.
Brain Res. 89:187-191, 1975.

OBSERVED NEUROTOXIC EFFECTS: Excitation of cells by compound was never enhanced by proline in the cortex, was occasionally potentiated in the cord, no effect in the cuneate nucleus. Authors conclude that proline may block compound as a synaptic transmitter but not as an excitant.

ANIMALS: Cats, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Proline 0.5-2 M at pH 7.5-9.0.

ROUTE AND SITE: Microinontophoresis, to neurons in 3 central nervous system areas; cortex, cord, and cuneate nucleus.

CONTROL INFORMATION: Laboratory controls.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemical

COMPOUND: Glutamic acid, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, ó-amino-ß-hydroxybutyric, glycine, α-alanine, ó-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

203<

COMPOUND: Glutamic acid, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

204<

COMPOUND: Glutamic acid, D-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuro-excitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-amino-isobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

205

COMPOUND: Glutamic acid, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

206

COMPOUND: Glutamic acid, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was equipotent to monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, N-acetyl

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, N-acetyl, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE
or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

2072

COMPOUND: Glutamic acid, 3-amino-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

208

COMPOUND: Glutamic acid, N-carbamoyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, N-(p-(((2,4-diamino-6-pteridinyl)methyl)methylamino) benzoyl)-,L-

000059052

REFERENCE: Greenhouse, A.H., Neubuerger, K.T. and Bowerman, D.L.
Arch. Neurol. 11:618-625, 1964.

OBSERVED NEUROTOXIC EFFECTS: Aphasia, right hemiparesis, convulsions; inflammatory lesions in left cerebral hemisphere attributed to direct toxic action of compound.

ANIMALS: 1 Human, F aged 36 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Active lymphosarcoma; 30 mg given, further doses not quantified.

ROUTE AND SITE: Intra-arterial, carotid

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 3 wk.

EXAM. TYPE: Behavior, histology (autopsy)

COMPOUND: Glutamic acid, N-(p-(((2,4-diamino-6-pteridnyl)methyl)methylamino) benzoyl),-L-

000059052

REFERENCE: Smith, B.
J. Neurol. Neurosurg. Psychiat. 38:810-815, 1975.

OBSERVED NEUROTOXIC EFFECTS: Destruction of oligodendrites and severe astrocytosis leading to death from therapy.

ANIMALS: Human autopsy material: 10 brains from treated leukemics.

PREPARATION AND DOSE or HISTORY OF PATIENT: 10, 12, or 12.5 mg/wk in addition to other drugs and radiotherapy.

ROUTE AND SITE: Intrathecal

CONTROL INFORMATION: Human autopsy material from 10 untreated leukemics.

DURATION OF EXPERIMENT: Therapy.

EXAM. TYPE: Histology

209<

COMPOUND: Glutamic acid, N,N-dimethyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, ô-amino-ß-hydroxybutyric, glycine, α-alanine, ô-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

210

COMPOUND: Glutamic acid, hydrazide, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-forminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, δ-amino-ß-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, beta-hydroxy

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-forminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, δ-amino-ß-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, N-methyl-, D-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

211<

COMPOUND: Glutamic acid, alpha-methyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

212

COMPOUND: Glutamic acid, alpha-methyl-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was toxic to non-neurol components (glia, etc.), but not to neurons.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, N-methyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, γ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, N-methyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

213

COMPOUND: Glutamic acid, N-methyl-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was more potent than monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuroexcitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

214

COMPOUND: Glutamic acid, alpha-methyl ester, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, gamma-methyl ester, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Knaape, H.H. and Wiechert, P. (In Ger.)
J. Neurochem. 17: 1171-1175, 1970.

OBSERVED NEUROTOXIC EFFECTS: EEG seizures followed injection into the hippocampus; other sites are ranked in order of decreasing sensitivity to compound, the ventricle being insensitive at doses used. The authors discuss the metabolism of compound as producing releasing factors for EEG seizures.

ANIMALS: 45 cats, 2.5-5 kg, surgically prepared

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-250 microliter in 10-15 sec

ROUTE AND SITE: Stereotactic injection into various cerebral regions

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Each up to about 30 min

EXAM. TYPE: Behavior, EEG

21 C7 A

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Lemkey-Johnston, N. and Reynolds, W.A.
J. Neuropath. Exp, Neurol. 33(1):74-97, 1974.

OBSERVED NEUROTOXIC EFFECTS: Tremors, and damage to dentate-hippocampal gyri surfaces. Involvement of retina and in the arcuate nucleus. Lesions in the tectum, habenular nuclei, subfornical organ, dorsolateral surface of the thalamus, cerebral cortex, area postrema, cuneatus and the nuclei gracilis. Death.

ANIMALS: 3 strains of Mice, Swiss-Albino - 7-10 days, and 1 mouse - A/Jax - ICR hybrid.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1, 2, or 4 mg/gm in 20% soln.

ROUTE AND SITE: I.P. and S.C.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Serial Sacr. 10 min to 48 hr.

EXAM. TYPE: Histology, Ultrastructural.

216

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Lemkey-Johnston, N., Butler, V. and Reynolds, W.A.
Expl. Neurol. 48:292-309, 1975.

OBSERVED NEUROTOXIC EFFECTS: Glutamic acid HCl at 2 mg/g produced lesions in arcuate nucleus (10 of 11 mice), also preoptic nucleus, tectum and pretectal area, subcommissural and subfornical organs and cerebellum (neuronal damage like that from MSG). Higher equivalency NaCl damaged mainly caudate-putamen, cerebellum, cortex, and habenula, related apparently to vascular changes. Sucrose produced vascular changes but no brain lesions.

ANIMALS: Mice, ICR or A/JAX-ICR hybrids, aged 4-12 d.

PREPARATION AND DOSE or HISTORY OF PATIENT: Glutamic acid HCl 2 and 4 mg/g as 20% solution; NaCl equimolar for Na to 1-10 mg/g MSG (0.31-3.12 mg/g); sucrose 14.6-36.5 mg/g as 80% solution, also equimolar to 4-10 mg/g MSG. Purpose: to test the components of MSG separately.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: None other than sucrose.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology, but timings and preparations are not described, though they reportedly influence the findings.

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Olney, J.W.
J. Neuropath. Exp. Neurol. 28: 455-474, 1969.

OBSERVED NEUROTOXIC EFFECTS: A single injection caused degeneration of the inner retinal cells of mice aged 9-10 days. There was evidence of edema of dendrites and cell bodies, mitochondria and several patterns of degeneration leading to necrosis.

ANIMALS: Over 200 mice, Swiss albino

PREPARATION AND DOSE or HISTORY OF PATIENT: 4 g/kg and other schedules

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: 30 min to 48 hr

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, monosodium salt, L-(+)-

000142472

REFERENCE: Olney, J.W.
Science 164:719-721, 1969.

OBSERVED NEUROTOXIC EFFECTS: (1) Selective destruction of: proptic and arcuate nuclei, some neurons in median eminence, subcommissural and subfornical organs, medial habenular nuclei, dentate gyrus. (2 and 3) Brain lesions found, not described. Chronic dosage: mainly non-neural studies, but stunting found in adenohypophysis.

ANIMALS: (1) Mice, Swiss albino, 10 litters aged 2-9 d
(2) Adult mice
(3) Neonatal C57BL/6 mice and albino rats

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5-4 mg/g, one dose; 20 dosed daily, for d 1-10 of age.
(2) 5-7 mg/g.
(3) ns.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: (1) 18 mice untreated.

DURATION OF EXPERIMENT: 1.9 mo.

EXAM. TYPE: Histology

2177

COMPOUND: Glutamic acid, monosodium salt, L-(+)-

000142472

REFERENCE: Olney, J.W. and Ho., O.
Nature 227:609-610, 1970.

OBSERVED NEUROTOXIC EFFECTS: Necrosis of hypothalamic neurons in mice given glutamate, aspartate, or cysteine, dose-related; zero damage from other compounds

ANIMALS: 75 Mice, Swiss Webster, age 10 d.

PREPARATION AND DOSE or HISTORY OF PATIENT: One of 10 amino acids and various other compounds, 2.5 or 10% in water, 0.25-2 g/kg.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Intubated, no treatment, 10 mice

DURATION OF EXPERIMENT: 5 hr.

EXAM. TYPE: Histology

218

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Olney, J.W.
J. Neuropath. Exp. Neurol. 30(1):75-90, 1971.

OBSERVED NEUROTOXIC EFFECTS: Hypothalamic lesions. Involvement of glial and ependymal cells. Arcuate (infundibular) nucleus and inner retinal neurons were destroyed. An identical pattern of neuronal necrosis can be induced by certain other amino acids, which have neuroexcitatory properties.

ANIMALS: 27 Mice, Webster Swiss, albino, 10 d post natal.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 18 m mole/kg in 10% aq soln.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 3 mice untreated, 3 mice: 18 m mole/kg sodium chloride.

DURATION OF EXPERIMENT: Sacr. 15 min to 8 d.

EXAM. TYPE: Histology, ultrastructure.

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Olney, J.W., Sharpe, L.G., and Feigin, R.D.
J. Neuropath. Exp. Neurol. 31(3): 464-488, 1972.

OBSERVED NEUROTOXIC EFFECTS: Cyanosis, vomiting, convulsions, neuron-necrotized hypothalamus, and brain lesions. Arcuate nucleus, medial habenular nucleus neurons, subfornical organ, cingulate cortex midline, anterior hippocamus (denate gyrus) and superior colliculus destroyed.

ANIMALS: 9 Rhesus Monkeys, (Macaca Mulatta), Infants.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1-4 g/kg admin. as 20cc/kg of skim milk water soln.

ROUTE AND SITE: Oral and S.C.

CONTROL INFORMATION: 3 monkeys treated with NaCl

DURATION OF EXPERIMENT: Serial sacr 3-5 hrs.

EXAM. TYPE: Ultrastructural, histology, cytopathology

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Olney, J.W., Ho, O.L., Rhee, V. and DeGubareff, T.
New Eng. J. Med. 289:1374-1375, 1973.

OBSERVED NEUROTOXIC EFFECTS: Brain lesions at junction of median eminence and arcuate-periventricular nucleus.

ANIMALS: Guinea-pigs, age 3 d

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 mg/g

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Guinea-pigs sodium chloride treated.

DURATION OF EXPERIMENT: 5 hr

EXAM. TYPE: Histology

219

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Perez, V.J. and Olney, J.W.
J. Neurochem. 19:1777-1782, 1972.

OBSERVED NEUROTOXIC EFFECTS: Arcuate nucleus, ventromedial hypothalamus and lateral thalamus were examined: control MSG level 25 mmol/kg dry weight, rose to 111 mmol in arcuat nucleus, 42 in ventromedial hypothalamus and lateral thalamus, at 3 hr, back to normal in 12-15 hr, blood (normal <1 mM) rose to 40 mM in 15 min, back to normal in 1-3 hr.

ANIMALS: 124 Mice, 18 litters, M and F, Swiss-Webster, aged 4 d

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2 mg/g

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Untreated mice, also zero time treated.

DURATION OF EXPERIMENT: 7.5 min to 18 hr, serial sacr.

EXAM. TYPE: Biochemistry

220

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Reynolds, W.A., Lemkey-Johnston, N., Filer, L.J., Jr. and Pitkin, R.M. Science 172: 1342-1345, 1971.

OBSERVED NEUROTOXIC EFFECTS: No morphological differences between treated and control hypothalami, but some tissue fixed inadequately resembled brain lesions.

ANIMALS: 16 Monkeys (M. mulatta and M. irus), infants

PREPARATION AND DOSE or HISTORY OF PATIENT: 1, 2, 4 g/kg, 50% soln in water.

ROUTE AND SITE: Nasogastric tube

CONTROL INFORMATION: 5 additional monkeys, water only.

DURATION OF EXPERIMENT: 6 hr

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, monosodium salt, L-(+)-
000142472

REFERENCE: Snapir, N., Robinzon, B. and Perek, M. Poultry Sci. 50:1511-1514, 1971.

OBSERVED NEUROTOXIC EFFECTS: Compound induced brain damage in the hypothalamus region surrounding the ventromedial area, leaving the hypothalamus itself unaffected.

ANIMALS: 84 Chicks, New Hampshire x White Leghorn, M, aged 5 d, in 6 grps.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 and 4 mg/g bw, one dose or daily

ROUTE AND SITE: S.C., back of neck

CONTROL INFORMATION: 2 grps saline

DURATION OF EXPERIMENT: 40 d after first dose

EXAM. TYPE: Histology

COMPOUND: Glutamic acid, sodium salt

REFERENCE: Fifkova, E., Van Harreveld, A.
Exp. Neurology 28:286-298, 1970.

OBSERVED NEUROTOXIC EFFECTS: (1) Transient arrest of electrogram of corpus striatum
(2) No noticeable effect on EEG.
Depolarizes neurons when app. electrophoretically may arrest all activity.

ANIMALS: (1) Chicks, Leghorn, 16 d incubation to hatching time.
(2) Chicks, 5 d after hatching.

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mM soln. of 1 sodium-glutamate, pH 7.2.

ROUTE AND SITE: I.V. at rate 1.2 ml/min for 1-5-2 min.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 16 d incubation-5 d old chicks.

EXAM. TYPE: Neurological.

221

COMPOUND: Glutamine, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

222

COMPOUND: Glutamine, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE
or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Glutamine, N,N-dimethyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutamine, N-methyl-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsel horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

223

COMPOUND: Glutaramide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl)-

000066819

REFERENCE: Segal, D.S., Squire, L.R. and Barondes, S.H.
Science 172:82-83, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound inhibits protein synthesis (translation) and long term memory, and produces initial hyperactivity. The effect of amphetamine on memory in the compound treated mice is not correlated with a measurable increase in activity. Studies using other compounds lead the authors to conclude that the block on memory was separate from the hyperactivity and was due to inhibition of protein synthesis.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT:
(1) 120 mg/kg
(2) 200 mcg
(3) Amt ns. followed 3 hr 45 min by amphetamine, 1 mg/kg, or saline.

ROUTE AND SITE: S.C. or Intracerebral

CONTROL INFORMATION: Controls saline treated.

DURATION OF EXPERIMENT: 3 hr

EXAM. TYPE: Behavior

224

COMPOUND: Glutaramide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxymethyl)

000066819

REFERENCE: Zech, R. and Domagk, G.F.
Brain Res. 86:339-342, 1975.

OBSERVED NEUROTOXIC EFFECTS: The compound inhibited the activity of the enzyme, noncompetitively and reversibly.

ANIMALS: In vitro human brain acetylcholinesterase

PREPARATION AND DOSE
or HISTORY OF PATIENT: Chemical enzyme inhibition system

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Glutaric acid

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, ß-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, ß-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: ß-alanine, GABA, taurine, N-methyl-ß-alanine, ä-amino-ß-hydroxybutyric, glycine, α-alanine, ä-aminovaleric, ß-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Glutaric acid, 2-oxo-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

225<

COMPOUND: Glutarimide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl)

REFERENCE: Segal, D.S., Squire, L.R. and Barondes, S.H.
Science 172:82-83, 1971.

OBSERVED NEUROTOXIC EFFECTS: Depression in activity from 1-4 hr after injection. Depression did not differ significantly from that produced by cycloheximide. No amnesic effect. Compound does not markedly inhibit cerebral protein synthesis. Authors conclude depression activity is unrealted to either amnesic action or to inhibition of cerebral protein synthesis.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: 200 mcg

ROUTE AND SITE: Intracerebrally

CONTROL INFORMATION: Controls saline treated

DURATION OF EXPERIMENT: At least 4 d.

EXAM. TYPE: Behavior, light discrimination tests.

226

COMPOUND: Glutarimide, 3-ethyl-3-methyl-

REFERENCE: Cohen, B., Rey-Bellet, J. and Bergman, P.S.
Neurology 10: 1024-1030, 1960.

OBSERVED NEUROTOXIC EFFECTS: Grand mal seizures were induced 33 times in 26 patients, psychomotor seizures in 2. The authors concluded that the compound was safe for EEG activation.

ANIMALS: 63 patients with definite brain disease

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10-915 mg, no other details

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical, EEG

COMPOUND: Gluterimide, 2-ethyl-2-phenyl-

000077214

REFERENCE: Ambre, J.J. and Fischer, L.J.
Res. Comm. Chem. Path. Pharm. 4: 307-326, 1972.

OBSERVED NEUROTOXIC EFFECTS: Treatment with compound resulted in a coma lasting about 36 hours. The intensity of the coma appeared to correlate to the plasma level of an unidentified major metabolite.

ANIMALS: Humans: 6 patients
Dogs: 4 healthy mongrels, 20 kg
Rats: M, S-D, 400 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: Humans: intoxicated by overdoses (1 case of 10 g reported)
Dogs: 400 mg/kg
Rats: 400 mg/kg

ROUTE AND SITE: Oral (humans); gavage (dogs, rats)

CONTROL INFORMATION: Humans, 3 healthy M, 70-84 kg, 1 g/subject orally

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Glutarimide, 2-ethyl-2-phenyl-

000077214

REFERENCE: Haas, D.C. and Marasigan, A.
J. Neurol. Neurosurg. Psychiat. 31: 561-564, 1968.

OBSERVED NEUROTOXIC EFFECTS: Cerebellar ataxia, organic mental changes, peripheral neuropathy

ANIMALS: Human: 3 F, 41-45

PREPARATION AND DOSE or HISTORY OF PATIENT: History of alcohol treated, replaced or supplemented with compound 1-4 g/d

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 2 mo to 8 yr (according to histories)

EXAM. TYPE: Clinical, electrophysiology

2272

COMPOUND: Gluterimide, 2-ethyl-2-phenyl-

000077214

REFERENCE: Melville, K., Jordon, G., Douglas, D.
Toxicology and Applied Pharmacology 9:363-375, 1966.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, complete surgical anesthesia in 3-6 hrs. Synergistic action with alcohol increased and hastened central nervous system depression and with increased dose produced surgical anesthesia.

ANIMALS: Mongrel dogs, 7.0-12.0 kg, M and F.

PREPARATION AND DOSE or HISTORY OF PATIENT: 100-300 mg/kg in total volumes of 50-8 ml water.

ROUTE AND SITE: Stomach tube

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: More than 1 wk.

EXAM. TYPE: Behavior

228

COMPOUND: Glycine, N-allyl-

REFERENCE: Horton, R.W. and Meldrum, B.S.
Br. J. Pharmac. 49: 52-63, 1973.

OBSERVED NEUROTOXIC EFFECTS: Seizures, photic stimulation, EEG changes, inhibition of brain glutamate carboxylase were caused by 3-mercaptopropionic acid more strongly than by allylglycine or 4-deoxypryidoxine HCl. Thus the authors concluded that seizures were due to depletion of glycine and γ-aminobutyric acid (GABA).

ANIMALS: Mice, CFW or BALB/C, M, 20-30 g
10 Baboons (Papio papio), adolescent, from Senegal, 3-6 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: ED_{50} and latency 1.0 mmol/kg, 160 min.
Baboons: ED_{50} and latency 4 mmol/kg, 100 min.

ROUTE AND SITE: Mice I.P., Baboons I.V.

CONTROL INFORMATION: Timed studies

DURATION OF EXPERIMENT. Various

EXAM. TYPE: Mice: behavior, biochemistry; baboons: polygraph.

COMPOUND: Glycine, N-allyl-

REFERENCE: Meldrum, B.S., Horton, R.W. and Brierley, J.B.
Brain 97:407-418, 1974.

OBSERVED NEUROTOXIC EFFECTS: Tonic-clonic seizures in varying degrees. Eventual brain damage in some. Selective changes in hippocampus and neocortex, later neuronal loss and gliosis; authors inferred medial temporal sclerosis.

ANIMALS: 13 Baboons: 9 P. papio and 4 P. cynocephalus, 3.4-6.6 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: 350-630 mg/kg in saline

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 42 d

EXAM. TYPE: EEG, histology, pathology

COMPOUND: Glycine, N-(gamma-glutamyl)-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

229

COMPOUND: Glycolic acid, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 8.9 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

230

COMPOUND: Gold

REFERENCE: Walsh, J.C.
Neurology 20:455-458, 1970.

OBSERVED NEUROTOXIC EFFECTS: Acute peripheral neuropathy, mainly sensory impairment, severe axonal degeneration in sural nerve.

ANIMALS: Human: one case, F, 63 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 3 doses in 2 wk of sodium aurothiomalate (44.5-46% Au) total 85 mg Au, for osteoarthritis.

ROUTE AND SITE: Inj.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 2 wk with follow-up, period ns.

EXAM. TYPE: Behavior, electrophysiology, histology (biopsy)

COMPOUND: Guanidine, (2-(hexahydro-1(2H)azocinyl)ethyl)-, sulphate (2:1)

000060026

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} >50 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Harrisite

REFERENCE: Satran, R.
Neurology 11: 928-932, 1961

OBSERVED NEUROTOXIC EFFECTS: Grand mal seizures, EEG paroxysmal bursts of moderate voltage spikes followed by high voltage waves, residual on overbreathing throughout test period. Inferred from review of literature to result from major component.

ANIMALS: Human: 3 cases, M, ages 22-32

PREPARATION AND DOSE
or HISTORY OF PATIENT: Chewed for 30 sec to 10 min

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 5 mo

EXAM. TYPE: EEG, clinical

231<

COMPOUND: HEF-2 (mix of alkylpentaborane derivatives)

REFERENCE: Feinsilver, L., Lawson, L.H., Berntson, L.G., Yevich, P.P. and Groff, W.A.
U.S. Army report CRDLR 3035, 1960.

OBSERVED NEUROTOXIC EFFECTS: Acute: ataxia, tremors, convulsions, hyperactivity on recovery; no lesions found in brain (dogs). Subacute: similar but less severe, guinea-pigs least severe; no lesions found (but dogs had increase of CSF). Concluded: Compound highly neurotoxic to central nervous system, speculatively inhibiting vital enzymes (but no ultrastructure was studied).

ANIMALS: Acute: dogs, beagle, M and F.
Subacute: rats, M, ages 8-10 wk; mice, F, 8-10 wk; dogs, beagle, M; guinea-pigs (no details).
Odor detection: 15 volunteers, human

PREPARATION AND DOSE
or HISTORY OF PATIENT: Acute: 6 or 9.5 ppm for 4 hr (dogs, grps of 3).
Subacute: 1.9 ppm 6 hr/d, 5 d/wk, 30 d (25 rats); same for 22 d (3 dogs); same for 31 d (10 guinea-pigs).
Odor detection: 0.41-26.1 ppm, time ns, median threshold 6.4 ppm.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Subacute: equal numbers untreated

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, behavior, histology

232<

COMPOUND: α-Hemolysin from Staphylococcus aureus

REFERENCE: Edelwejn, Z., Jeljaszewicz, J., Szmigielski, S. and Zak, C.
Tox. Appl. Pharm. 13:133-145, 1968.

OBSERVED NEUROTOXIC EFFECTS: "Collapse of the brain bioelectric activity" (EEG tracings), partly prevented by antagonist. Compound interpreted to disturb repolarization of stimulated neurons.

ANIMALS: 20 Rabbits, Polish lowland, M, 3 kg, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 mcg/kg of purified compound with/without an antagonist (p-chlorophenoxyacetic acid-dimethylaminoethyl chlorohydrate, centrophenoxine) on various schedules.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Recordings before test

DURATION OF EXPERIMENT: About 6 d.

EXAM. TYPE: EEG

COMPOUND: (-)-Heptadeca-trans-8,10,12-Triene-4,6-Diyne-1,14-Diol

000505759

REFERENCE: Starreveld, E. and Hope, C.E.
Neurology 25:730-734, 1975.

OBSERVED NEUROTOXIC EFFECTS: Muscarinic effects, convulsions, "diffusely abnormal" EEG, hypoxia, metabolic acidosis.

ANIMALS: Human: 1 case-report, M, age 54.

PREPARATION AND DOSE or HISTORY OF PATIENT: Ate 2 bites of root, thinking plant to be type of parsnip.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 11 d

EXAM. TYPE: Clinical, EEG, hospital laboratory

COMPOUND: Heptanedioic acid, 4-amino-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

233

COMPOUND: Heptanedioic acid, 2-amino-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

234

COMPOUND: Heptanedioic acid, 2-amino-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE
or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Heptanedioic acid, 2,5-diamino-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Hexane
000110543

REFERENCE: Herskowitz, A., Ishi, N. and Schaumberg, H.
New Eng. J. Med. 285:82-85, 1971.

OBSERVED NEUROTOXIC EFFECTS: Weakness and sensory loss after 2-4 mo., dose-related, peripheral nervous system demyelination and axonal degeneration, denervation of muscles, slow clinical recovery. Authors recommend that current safety limit of 500 ppm be reduced to 100 ppm as in Japan.

ANIMALS: Human: 3 cases, F, age 27-47.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure to 650-1300 ppm in air, industrially.

ROUTE AND SITE: Inhalation, cutaneous, oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Over 6 mo.

EXAM. TYPE: Clinical, electrophysiology, histology (biopsy), biochemistry

235

COMPOUND: Hexanedioic acid, 2-amino-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

236

COMPOUND: Hexanedioic acid, 2-amino-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Hexanedioic acid, 2-amino-, DL-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was toxic to non-neurol components (glia, etc.), but not to neurons.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: 2,5-Hexanedione

REFERENCE: Raleigh, R.L., Spencer, P.S. and Schaumburg, H.H.
J. Occup. Med. 17:286, 1975. (Letter to Editor)

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy observed in both groups.

ANIMALS: Rats

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Av. dose 340 mg/kg/d, 5d/wk for 19 wk.
(2) Av. 25 ml of 0.5% soln, 520 mg/kg/d for 2 mo.

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: (1) 19 wk (2) 2 mo.

EXAM. TYPE: ns.

2372

COMPOUND: 2,5-Hexanedione

REFERENCE: Spencer, P.S. and Schaumburg, H.H.
J. Neurol. Neurosurg. Psychiat. 38:771-775, 1975.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy with dying-back peripheral and central nervous system degeneration; giant axonal swelling and massed neurofilaments.

ANIMALS: 6 rats, S-D, 400 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 0.1 ml/rat/d, 5 d/wk for 13 wk or
(2) 0.2 or 0.4 ml/rat/d for 6-10 wk,
Mean total was equivalent to 340 mg/kg/d.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Up to 13 wk

EXAM. TYPE: Behavior, histology

238

COMPOUND: 2-Hexanone

000591786

REFERENCE: Allen, N., Mendell, J.R., Billmaier, D.J., Fontaine, R.E. and O'Neill, J. Arch. Neurol 32:209-218, 1975.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy: distal, motor, and sensory disorder with minimal reflex loss. Muscle weakness and sensory loss most common in hands and feet. No evidence of autonomic dysfunction observed.

ANIMALS: 86 cases in 1,157 employees screened at a factory in Ohio.

PREPARATION AND DOSE or HISTORY OF PATIENT: Workers in plant producting plastic-coated and color-printed fabrics. Methyl n-butyl Ketone was implicated as causative agent on the basis of correlation with exposure, with incidence and severity of disease, and temporal course of out break. Exposure to 36 ppm in air for over 42 hr/wk. Synergistic effect with methyl ethyl ketone or other chemicals possible.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: Investigative (questions and answers), retrospective

DURATION OF EXPERIMENT: Approx. 1 yr.

EXAM. TYPE: Clinical and electrodiagnostic

COMPOUND: 2-Hexanone

000591786

REFERENCE: Billmaier, D., Yee, H.T., Allen, N., Craft, B., Williams, N., Epstein, S. and Fontaine, R. J. Occup. Med. 16:665-671, 1974.

OBSERVED NEUROTOXIC EFFECTS: All workers screened for nerve conduction and electromyography, 192 referred for study, 68 with definite peripheral neuropathy, 28 more suspected, 6 severe. Sural nerve biopsies normal. Part-recovery in 6 mo. or more, severe cases.

ANIMALS: Human: 1157 workers at a coated fabrics plant.

PREPARATION AND DOSE or HISTORY OF PATIENT: Of approx 275 chemicals MBK was suspected (timing of use and of cases) but methyl ethyl ketone and phthalate esters were not ruled out. Cases centered on print-shop, were related to work-load and to eating at work.

ROUTE AND SITE: Inhalation, skin contact, ingestion considered.

CONTROL INFORMATION: Sought but not rigorously established.

DURATION OF EXPERIMENT: Ongoing

EXAM. TYPE: Electrophysiology, behavior, biopsy, clinical, laboratory.

COMPOUND: 2-Hexanone

000591786

REFERENCE: Duckett, S., Williams, N. and Francis, S.
New Eng. J. Med. 290:1264, 1974.

OBSERVED NEUROTOXIC EFFECTS: Sciatic nerves axonal edema, degeneration associated with secondary myelin breakdown.

ANIMALS: (1) 9 rats, (2) 8 rats

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 200 ppm in air, 8 hr/d, 5 d/wk, for 6 wk.
(2) same plus methyl-ethyl ketone 2000 ppm.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 6 wk

EXAM. TYPE: Histology

239

COMPOUND: 2-Hexanone

000591786

REFERENCE: McDonough, J.E.
New Eng. J. Med. 290:695, 1974. (Letter to Editor)

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy

ANIMALS: 6 rats

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1300 ppm in air, 6 hr/d, 5 d/wk, 4 mo. (TLV is 100 ppm = 410 mg/m^3).

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 4 mo.

EXAM. TYPE: ns.

240>

COMPOUND: 2-Hexanone

000591786

REFERENCE: Mandell, J.R.,
New Eng. J. Med 290: 1263-1264, 1974.

OBSERVED NEUROTOXIC EFFECTS: 182 employees with abnormal electrophysiology, 79 with clinical polyneuropathy, peripheral, related epidemiologically to exposure. Chickens had signs of nerve damage after 35 d at 200 ppm, cats at 33 d and rats at 60 d of 400-600 ppm. Limb weakness, slow conduction, swollen axons, demyelination. Rat and human exposures were seen as "remarkably close" in duration.

ANIMALS: 1. Human: 1161 industrial employees
2. Rats, cats, chickens

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1. Exposure, 8-12 hr/d 22-24 d/mo for 9 mo. total 1584-2592 hr.
2. 200-600 ppm 24 hr/d, 7 d/wk, 60 d for total 1440 hr exposures.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, behavior, histology

COMPOUND: 2-Hexanone

000591786

REFERENCE: Mandell, J.R., Saida, K., Ganansia, M.F., Jackson, D.B., Weiss, H., Gardner, R.W., Chrisman, C., Allen, N., Couri, D., O'Neill, J.
Science 185:787-789, 1974.

OBSERVED NEUROTOXIC EFFECTS: Hindlimb then forelimb weakness in animals, increased water intake, slow nerve conduction in cats, with disturbed patterns, demyelination and axonal degeneration in animals.

ANIMALS: 5 Chickens, domestic
4 Rats, S-D
4 Cats, domestic

PREPARATION AND DOSE
or HISTORY OF PATIENT: All groups exposed 24 hr/d for 2 mo., total 1440 hr.
Chickens: 200 ppm in air, reduced to 100 ppm.
Rats: 600 ppm reduced to 400 ppm.
Cats: 600 ppm reduced to 400 ppm.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Pair-fed matched controls

DURATION OF EXPERIMENT: 2 mo., on going

EXAM. TYPE: Behavior, electorphysiology, histology.

COMPOUND: 2-Hexanone

000591786

REFERENCE: Raleigh, R.L., Spencer, P.S. and Schaumburg, H.H.
J. Occup. Med. 17:286, 1975 (Letter to Editor)

OBSERVED NEUROTOXIC EFFECTS: (1) No evidence of clinical neuropathy. Minimal histologic changes in nerve fibers in cats treated with 330 ppm for 4.5 months, not seen in 100 ppm group. Histological exam of rats incomplete to date. (2) Clinical neuropathy seen. (3) Clinical neuropathy was not produced.

ANIMALS: (1) Cats, rats (2) Cats and dogs (3) Guinea pigs

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 330 ppm and 100 ppm for 6 hr/d, 5d/wk for 5 mo.
(2) 150 mg/kg, 2/d, 5d/wk for 2 mo(cat) 2-4 mo dogs.
(3) Amt ns., repeated applications over period of 8 mo.

ROUTE AND SITE: (1) Inhalation (2) S.C. (3) Top. Sk.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, histological

241<

COMPOUND: HiCal-2

REFERENCE: Feinsilver, L., Lawson, L.H., Yevich, P.P. and Jacobson, K.H.
U.S. Army CWL Report CWLR 2367, 1960.

OBSERVED NEUROTOXIC EFFECTS: LC_{50} under conditions were:
Rats-103 mg/m^3; mice-96 mg/m^3. Signs included ataxia, depression, prostration, tremors, clonic convulsions, interpreted as "marked effect upon" the central nervous system.

ANIMALS: Rats, ages 8-10 wk, M
Mice, 8-10 wk, F
Dogs, beagle, M.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposed to vapors of compounds in LC_{50} study, 2-4 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Observation to 7 d after exposure

EXAM. TYPE: Behavior, pathology

242

COMPOUND: Holothurin A

REFERENCE: Thron, C.D., Durant, R.C. and Friess, S.L.
Tox. Appl. Pharm. 6:182-196, 1964.

OBSERVED NEUROTOXIC EFFECTS: Lower concentrations produced tissue responses that were "largely irreversible," loss of excitability, and blocks of nerve conduction. Interaction of this animal saponin with chemoreceptors in nerve and neuromuscular tissues is discussed.

ANIMALS: In vitro nodes of Ranvier from desheather sciatic nerves of frog (R. pipiens), and rat phrenic nerve-diaphragm preparations

PREPARATION AND DOSE or HISTORY OF PATIENT: 5.64×10^{-10} to 10^{-4} M in medium, applied for brief periods.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Zero application.

DURATION OF EXPERIMENT: Up to about 1 hr.

EXAM. TYPE: Electrophysiology

COMPOUND: D-Homocysteic acid

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: DL-Homocysteic acid

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

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PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

2423

COMPOUND: DL-Homocysteic acid

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was more potent than monosodium glutamate in necrosing neurons in the retina and brain. This compound is a powerful neuro-excitant and the neurotoxic properties may be governed by similar mechanisms.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

244

COMPOUND: L-Homocysteic acid

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

COMPOUND: Hydantoin, 5,5-diphenyl- (Phenytoin)

000057410

REFERENCE: Ahmad, S., Laidlaw, J., Houghton, G.W. and Richens, A.
J. Neurol. Neurosurg, Psychiat. 38:225-231, 1975.

OBSERVED NEUROTOXIC EFFECTS: Intoxication confirmed by serum phenytoin levels. Choreoathetoid movements typical. In 3 cases intoxication resulted from drug interactions.

ANIMALS: Human: 4 cases (m 19, F 34, F 28, F 61) epileptics

PREPARATION AND DOSE or HISTORY OF PATIENT: Usual dose 300 g/d long term

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Years

EXAM. TYPE: Clinical, EEG, blood chemistry

COMPOUND: Hydantoin, 5,5-diphenyl-

000057410

REFERENCE: Dam, M.
Acta Neurol. Scand. 42:491-494, 1966.

OBSERVED NEUROTOXIC EFFECTS: Severe ataxia, uncertain gait, difficulty in turning, falling. Attacks recalled brain stem attacks with tonic convulsions in legs in one pig. One showed nystagmus. Cerebellum had altered Purkinje cells swollen in 1 pig, shrunken and swollen in other. Loss of ganglion cells with empty synapses.

ANIMALS: 3 Pigs, 20 kg, litter-mates

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 10 mg/kg followed by increasing doses for 3 mo.
(2) As above, except starting with 20 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 1 pig untreated

DURATION OF EXPERIMENT: Approx. 3 mo.

EXAM. TYPE: Histological and chemical

245

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: del Cerro, M.P. and Snider, R.S.
Neurology 17:452-466, 1967.

OBSERVED NEUROTOXIC EFFECTS: Severely ataxic at time of sacrafice. Ultrastructure study. Lamellar concentric bodies typical of lipoidoses throughout cerebellar cortex but most affecting Purkinje cells. Some myelinated axons were altered.

ANIMALS: 30 Rats, Wistar, adult M, 200 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/d, 5 d/wk for 1 wk, then 20 mg/d, then 30 mg/d, then 40 mg/d for 5 d/wk till death or sacrifice. Elsewhere authors state drug discontinued after 10 wk in animals kept for 6 mo.

ROUTE AND SITE: I.M.

CONTROL INFORMATION: 2 Control groups: solvent only and no treatment.

DURATION OF EXPERIMENT: Serial sacr to 6 mo.

EXAM. TYPE: Histology

246

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Hofmann, W.W.
Neurology 8:210-214, 1958.

OBSERVED NEUROTOXIC EFFECTS: Cerebellum: Purkinje cells "virtually disappeared," attributed by author partly to the drug. But cause of seizures was not found.

ANIMALS: Human: 1 F, 28 yr, with multiple seizures of sudden onset.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 250 mg/4 hr for 4 d, then taper off, but seizures recurred, and 250 mg/4-6 hr reinstituted, Patient died after 16 d.

ROUTE AND SITE: I.V. 1 dose, then I.M.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 16 d

EXAM. TYPE: Autopsy

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Kooiker, J.C. and Sumi, S.M.
Neurology 1:68-71, 1974.

OBSERVED NEUROTOXIC EFFECTS: Choreoathetoid symptoms that disappeared with falling serum levels of drug and did not recur when patients took the prescribed intake (300 mg/d) and no more.

ANIMALS: Humans: 2 case-reports of adverse drug reaction

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) prescribed 300 mg/d, sometimes took more; serum level was 40 mcg/ml.
(2) prescribed 300 mg/d; serum level was 64-68 mcg/ml.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Follow-up reported: (1) 21 mo; (2) 12 d

EXAM. TYPE: Clinical, laboratory, EEG

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Kutt, H., Winters, W., Kokenge, R. and McDowell, F.
Arch. Neurol. 11:642-648, 1964.

OBSERVED NEUROTOXIC EFFECTS: Diphenylhydantoin blood levels (thus ability to metabolize) related to side-effects: nystagmus at 20, ataxia at 30 mental changes at 40 mcg/ml of blood.

Extent of mental changes varied widely, with lethargy and inability to concentrate were the most frequent manifestations.

ANIMALS: Human, 32 patients

PREPARATION AND DOSE or HISTORY OF PATIENT: 4-10 mg/kg/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Long-term, not described

EXAM. TYPE: Clinical

>237<

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Kutt, H., Wolk, M., Scherman, R. and McDowell, F.
Neurology 14: 542-548, 1964.

OBSERVED NEUROTOXIC EFFECTS: Nystagmus, ataxia and other signs correlated with accumulations of unmetabolized compound owing to low activity of liver production of metabolite, which appeared to the authors to be a genetically determined deficiency.

ANIMALS: Human: 2 of 4 siblings and a mother of a healthy family

PREPARATION AND DOSE or HISTORY OF PATIENT: Usual dosage of about 4 mg/kg and smaller dosages. Experimentation with an important parahydroxylated metabolite, 5-phenyl-5'-parahydroxyphenylhydantoin, normally resulting from enzymatic reaction in liver.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Described

DURATION OF EXPERIMENT: About 5 wk

EXAM. TYPE: Metabolic, genetic, clinical

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Lovelace, R.E. and Horwitz, S.J.
Arch. Neurol. 18:69-77, 1968.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy in 26, absent deep tendon reflexes in legs (both knee and ankle in 19), related slow nerve conduction. More frequent in those treated>10 yr, but amount of dose no guide. Slow conduction considered an early-warning of neuropathy from compound.

ANIMALS: Humans: 50 selected epileptics age-range 12-50 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: 200-600 mg for 5-26 yr.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, electrophysiology

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Morrell, F., Bradley, W. and Ptashne, M.
Neurology 8: 140-144, 1958.

OBSERVED NEUROTOXIC EFFECTS: The compound raised the threshold for response to electrical stimulus, decreased the spike amplitude in A fibers, abolished "nerve repetition" and reversed the effects of oxalate.

ANIMALS: 48 Rabbits, 2-3.5 kg, prepared surgically.

PREPARATION AND DOSE or HISTORY OF PATIENT: Peripheral nerve preparation in situ, doses ns.

ROUTE AND SITE: I.V. or I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns,but in one test 90 min.

EXAM. TYPE: Electrophysiology

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Norris, F.H., Colella, J. and McFarlin, D.
Neurology 14: 869-876, 1964.

OBSERVED NEUROTOXIC EFFECTS: Of human cases, 2 took massive doses, and 1 had B_{12} deficiency; neuromuscular transmission was disordered. Competitive neuromuscular blockade appeared to result from either end-plate depolarization or anticholinesterase activity.

ANIMALS: (1) Human: 3 cases
(2) Rats: 150-360 g, sciatic nerve and anterior tibial and peroneus longus preparations

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Up to 26 mg/kg
(2) 10 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electromyography, clinical chemistry

249

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Riehl, J-L. and McIntyre, H.B.
Neurology 18:1107-1112, 1968.

OBSERVED NEUROTOXIC EFFECTS: EEG: slowing and/or increased amplitude only in zone(s) of abnormalities, not in unaffected zones nor in control subjects.

ANIMALS: Humans: 5F, 3 M, ages 18-60 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Epileptics with abnormal EEG and no history of drug use. 50 mg/2 min to total 250 mg.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Added: 3 volunteers, M 25, F 48, 55, not epileptics yr.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: EEG

250

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Roseman, E.
Neurology 11: 912-920, 1961

OBSERVED NEUROTOXIC EFFECTS: Toxicity manifested by Dilantin "drunkenness" accompanied by EEG changes illustrated in detail, from slow alpha to marked delta activity. Author suggests these as index for managing dosage of Dilantin in difficult cases.

ANIMALS: Human: 4 cases, 2-24 yr old

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1 g (infants) to 0.4-0.6 g (adults) per d, judged by results to be maximal effective dosage (not minimal).

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to about 3 mo

EXAM. TYPE: Clinical, EEG

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Selhorst, J.B., Kaufman, B. and Horwitz, S.J.
Arch. Neurol. 27:453-455, 1972.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, cerebellar damage. Not reversed after discontinuation of drug for up to 4 yr.

ANIMALS: 2 Humans, F aged 16, M aged 11 with epilepsy.

PREPARATION AND DOSE or HISTORY OF PATIENT: Histories of 300-1000 mg/d for 28 mo. and 9.5 yr.

ROUTE AND SITE: Oral

CONTROL INFORMATION: No controls

DURATION OF EXPERIMENT: 28 mo; 9.5 yr (histories)

EXAM. TYPE: Electrophysiological, radiological

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Theil, G.B., Richter, R.W., Powell, M.R. and Doolan, P.D.
Neurology 11: 138-142, 1961.

OBSERVED NEUROTOXIC EFFECTS: Prolonged restless coma with cycles of responsiveness. Hemodialysis after 138 hr thought to have prevented worse damage. Residual frontal-lobe damage suspected after 1 yr. Male infant born during treatment appeared normal at birth and after 1 yr.

ANIMALS: Human: one F, age 18, pregnant 8 mo

PREPARATION AND DOSE
or HISTORY OF PATIENT: 21.5 g one dose (attempted suicide)
History of grand-mal, schizophrenia

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Behavior, EEG, clinical

251 A

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Wstepne, D.
Neur. Neurochir. Pol. 8: 427-431, 1974.

OBSERVED NEUROTOXIC EFFECTS: Disseminated changes in neurons, and demyelination of white matter of cerebral hemispheres. EEG showed modified spindles in frontal leads, interpreted as nonpathological. Chronic dose produced blood level of 10-20 mcg/ml.

ANIMALS: 8 cats

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15-20 mg/kg for "several months to 1 year"
2 cats: 10-15 mg/kg I.V. one dose

ROUTE AND SITE: Oral, I.V.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: EEG and evoked potentials, histology

252

COMPOUND: Hydantoin, 5,5-diphenyl

REFERENCE: Yanagihara, T. and Hamberger, A.
Exp. Neurol. 32:152-162, 1971.

OBSERVED NEUROTOXIC EFFECTS: Amino acid incorporation into proteins of cerebral cortex: in neurons inhibited quickly with recovery, in neuroglia prolonged inhibition; perikarya (mainly nuclei) responded sensitively and neuro-suppressively.

ANIMALS: Rats, S-D, F, 150-170 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 80-300 mg/kg/d, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 12 d

EXAM. TYPE: Biochemistry

COMPOUND: Hydantoin, 5,5-diphenyl-monosodium salt (Dilantin)

000630933

REFERENCE: Kokenge, R., Kutt, H., McDowell, F.
Neurology 15:823-829, 1965.

OBSERVED NEUROTOXIC EFFECTS: (1) Nystagmus ataxia, stuporous, disoriented.
(2) High blood & tissue levels of Dilatin which can damage neural tissues, loss of Purkinje cells & occurrence of edema of Bergmann's glial layer.

ANIMALS: (1) Human, 18 yrs, 66 kg.
(2) 36 rats, Albino, 200 gm
(3) Cats

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 300 mg Dilantin, 90 mg phenobarbital, 500 mg primidone, 20 mg Librium daily. Dilantin may have been increased to 900-1000 mg and phenobarbital 300 mg.
(2) 10, 20, 30, 50, 75, 100, 150 mg/kg daily for 15-30 d.

ROUTE AND SITE: (1) Oral (2) I.M.

CONTROL INFORMATION: (3) Cats

DURATION OF EXPERIMENT: (1) 15 yr (2) 15 d

EXAM. TYPE: Neurological

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)- (Nitrofurantoin)
000067209

REFERENCE: Asbury, A.K.
Lancet 1:334-335, 1963.

OBSERVED NEUROTOXIC EFFECTS: Polyneuropathy reported after nitrofurantoin in presence of renal impairment claimed to be secondary to renal impairment, as here, where no nitrofurantoin was given.

ANIMALS: Human: 4 cases, M, details ns.

PREPARATION AND DOSE or HISTORY OF PATIENT: No treatment with compound.

ROUTE AND SITE: Nil

CONTROL INFORMATION: This group

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Autopsy (pathology)

253

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Behar, A., Rachmilewitz, E., Rahamimoff, R. and Denman, M.
Arch. Neurol. 13:160-163, 1965.

OBSERVED NEUROTOXIC EFFECTS: Sciatic and brachial nerves showed axonal dystrophy in all treated rats, sciatic showed increased chronaxis and decreased conduction velocity; all related to amount and duration of treatment.

ANIMALS: 83 Rats, Sabra, M and F

PREPARATION AND DOSE or HISTORY OF PATIENT: 20, 50, 100 mg/kg/d in divided doses (2/d) for 2, 4, 6, 8 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 20 Rats

DURATION OF EXPERIMENT: Serial sacr to 8 d.

EXAM. TYPE: Blood chemistry, electrophysiology, histology

254

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Ellis, F.G., Lond, M.S.
Lancet ii:1136-1138, 1962.

OBSERVED NEUROTOXIC EFFECTS: Peripheral (limb) polyneuritis progressive till death or cessation of compound; part-recovery over long time. No histology performed.

ANIMALS: 6 Humans, M, 53-79 years with renal impairment.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 300-400 mg/d for 4 wk to 7 mo.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Honet, J.C.
Arch. Phys. Med. Rehab. 48: 209-212, 1967.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy with denervation of limb extremities.

ANIMALS: Human: one F, 43, 32.2 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: 800 mg/d for 1 wk and then 400 mg/d for 3 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Hospital stay 9 d

EXAM. TYPE: Clinical, electromyography

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Lindholm, T.
Neurology 17:1017-1020, 1967.

OBSERVED NEUROTOXIC EFFECTS: Electromyographical signs of peripheral muscle denervation in 23 (62%) treated, 2 (18%) controls; only 5 treated subjects had behavioral (clinical) signs.

ANIMALS: Human: 43 F, 5 M with urinary infections but not uremia. Treated group: 33 F, 4 M (ages 12-70 yr, av. 43).

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-300 (av. 115) mg/d, total 0.7-77.1 (av. 15.8) g.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 10 F, 1M (ages 20-64 yr, av. 46) untreated.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, behavior

255

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Loughridge, L.W.
Lancet ii:1133-1135, 1962.

OBSERVED NEUROTOXIC EFFECTS: Blood level 5.1-6.5 mcg/ml vs. normal 1.8 in similarly treated patients. Peripheral neuropathy (limbs) diagnosed during life; Median nerves swollen, atrophic, with Wallerian degeneration.

ANIMALS: 1 Human: M, 54, with renal failure

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg, 3/d for 6 wk.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Approx. 7 wk.

EXAM. TYPE: Clinical, blood-chemistry, histology (autopsy)

256

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Morris, J.S.
J. Neurol. Neurosurg. Psychiat. 29: 224-228, 1966.

OBSERVED NEUROTOXIC EFFECTS: Signs of peripheral neuropathy (paralysis, muscle-wasting) that were only partly reversible after discontinuing medication.

ANIMALS: Human: 4 cases aged 36-75, M and F

PREPARATION AND DOSE
or HISTORY OF PATIENT: Total doses: 8-1000 g over time

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 2-6 mo

EXAM. TYPE: Clinical

COMPOUND: Hydantoin, 1-(5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Rubenstein, C.J.
J. Am. Med. Assn 187:647-649, 1964.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, mainly of lower limbs, expecially in presence of renal impairment; recovery if muscle weakness not severe. Wallerian degeneration in myelin sheaths.

ANIMALS: 5 Humans, M, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 300-600 mg/d for 10 d to several yr.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 10 d to several yr.

EXAM. TYPE: Clinical, histology

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Toole, J.F. and Parrish, M.L.
Neurology 23:554-559, 1973.

OBSERVED NEUROTOXIC EFFECTS: Symptoms began usually within 45 d, progressed in pattern of ascending sensorimotor polyneuropathy. Degree of recovery related to symptoms severity but not to dose, nor to continuance of drug despite symptoms. Recovery took days to 7 mo., deaths were not drug-related. 20% of lumbar punctures showed high protein. Demyelination, axonal chromatolysis, but no inflammation.

ANIMALS: Humans

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.0-100+ g during 7-196 d. 137 patients in world literature, reports assembled and analyzed.

ROUTE AND SITE: Oral (I.V. in one, instilled into bladder in two, into pleura in one).

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 196 d

EXAM. TYPE: Behavior, laboratory, histology

257A

COMPOUND: Hydantoin, 1-((5-nitrofurfurylidene)amino)-
000067209

REFERENCE: Toole, J.F., Gergen, J.A., Hayes, D.M., and Felts, J.H.
Arch. Neurol. 18:680-687, 1968.

OBSERVED NEUROTOXIC EFFECTS: Changes in sensory and motor nerve conduction velocities; no related changes in blood or urine.

ANIMALS: Human healthy volunteers, 7 M, 7F, ages 22-38 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg with meals and at bedtime for 14 d

ROUTE AND SITE: Oral

CONTROL INFORMATION: Placebo, double-blind

DURATION OF EXPERIMENT: 6 wk

EXAM. TYPE: Physical; bloods and urine

258

COMPOUND: Hydrazine, 1,1-dimethyl-

000057147

REFERENCE: Cornish, H.H. and Barth, M.L.
Tox. Appl. Pharm. 6:568-575, 1964.

OBSERVED NEUROTOXIC EFFECTS: Tremors followed by tonic-clonic convulsions; increased urinary amino acid excretion, no change of brain sulfhydryl levels, no observed tissue pathology.

ANIMALS: Rats, S-D, M, 225-275 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 60-120 mg/kg; 100 mg/kg was LD_{50} 80 mg/kg was dose most used.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Mentioned, not described.

DURATION OF EXPERIMENT: Up to 10 d

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Hydrazine, 1,1-dimethyl-

000057147

REFERENCE: Rinehart, W.E., Donati, E. and Greene, E.A.
U.S. Army CCRDC Report CRDLR 3047, 1961.

OBSERVED NEUROTOXIC EFFECTS: Compound used in guided-missile systems, known central nervous system stimulant; aim of study was to learn MAC for prolonged exposure. Toxic effects seen included tremors, convulsions, death. Mild signs seen in dogs exposed to 5 ppm 26 wk. No lesions in central nervous system reported. Conclusion: MAC for man should be "well below 5 ppm" and 0.5 ppm was suggested.

ANIMALS: (1) 60 Mice, CS1, F, 20-30 g
(2) 50 Rats, Wistar CRDL, M, 200 g
(3) 6 Dogs, beagle, M, 11.4 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-140 ppm of air (12.2-342 mg/m^3) for 6-26 wk
(1&2) 140 ppm 6 wk and 75 ppm 7 wk
(3) 25 ppm 13 wk and 5 ppm 26 wk.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Untrtd animals in all experiments

DURATION OF EXPERIMENT: At least 9 mo.

EXAM. TYPE: Behavior, pathology-histology

COMPOUND: Hydrazine, hydrochloride

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2.5 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

259<

COMPOUND: Hydrazine, (alpha-methylphenethyl)-, hydrochloride

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} 20 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

260K

COMPOUND: Hydrazine, phenethyl-, hydrochloride

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 20 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Hydrazoic acid

007782798

REFERENCE: Graham, J.D.P., Rogan, J.M. and Robertson, D.G.
J. Indust. Hyg. Toxicol. 30(2):98-102, 1948.

OBSERVED NEUROTOXIC EFFECTS: Respiratory stimulation followed by depression; generalized convulsion with or without recovery. Central nervous system not examined.

ANIMALS: Mice, Rats, Guinea-pigs, Rabbits (no details)

PREPARATION AND DOSE or HISTORY OF PATIENT: Lethal and sublethal doses mentioned, no details.

ROUTE AND SITE: Inj., inhalation.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, body-counts

COMPOUND: Hydrocyanic acid

000074908

REFERENCE: Ibrahim, M.Z.M. and Levine, S.
J. Neurol. Neurosurg. Psychiat. 30: 545-555, 1967.

OBSERVED NEUROTOXIC EFFECTS: As a result of studies of fixation-artifacts, differences among artifacts were found when rats had been intoxicated with cyanide. Authors concluded that oligodendroglial proliferation in central nervous system was closely related in time to earliest detectable photomicroscopic changes in myelin produced by the compound.

ANIMALS: 27 rats, Lewis, young adult, M & F

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure to compound for 20-30 min, sacrificed by overdose of same

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: 7 other rats, untrtd, killed by other methods

DURATION OF EXPERIMENT: Serial to 80 d

EXAM. TYPE: Histology, histochemistry

261<

COMPOUND: Hydrocyanic acid

000074908

REFERENCE: Levine, S. and Stypulkowski, W.
Neurology 9: 407-411, 1959.

OBSERVED NEUROTOXIC EFFECTS: The distribution of hydrogen cyanide lesions could be reproduced by ligation alone. The authors concluded that ischemia was the mechanism of cyanide encephalopathy.

ANIMALS: Rats, Wistar, F, 160 or 225 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: Exposure for 25-35 min in inhalation jars; half of each group given unilateral ligation of common carotid.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Ligation or no

DURATION OF EXPERIMENT: About 4 d after exposure

EXAM. TYPE: Histology

COMPOUND: Hydrogen selenide
007783075

REFERENCE: Buchan, R.F.
Occup. Med. 3:439-456, 1947.

OBSERVED NEUROTOXIC EFFECTS: Nausea, vomiting, dysgeusia, dizziness, lethargy; gradual recovery over 6 mo. after removal of selenium source.

ANIMALS: Human: 5 case who complained, selected from 25 exposed industrially

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure not measurable (below 0.2 ppm) because methods admitted to be insensitive. Urine av 6.16 mcg/100 ml (range 0-13.1). Source (ink) contained 52 mg/liter as selenious acid. Odor identified by investigators.

ROUTE AND SITE: Inhalation, perhpas other routes too.

CONTROL INFORMATION: Yes, but later found to have been exposed.

DURATION OF EXPERIMENT: About 1 mo.

EXAM. TYPE: Urinalysis, clinical

COMPOUND: Hydrogen sulfide
007783064

REFERENCE: Adelson, L. and Sunshine, I.
Arch. Path. 81:375-380, 1966.

OBSERVED NEUROTOXIC EFFECTS: Rapid and complete central nervous system paralysis, fatal.

ANIMALS: Human: 3 M, ages 21-32

PREPARATION AND DOSE or HISTORY OF PATIENT: Industrial exposure to high concentrations of gas, probably over 0.1-0.2%.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Autopsy

COMPOUND: Imidazole

000288324

REFERENCE: Nishie, K., Waisa, A.C. and Keyl, A.C.
Tox. Appl. Pharm. 41:301-307, 1969.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, varying degrees of tremor, opisthotonus and tonic extensor seizures. Authors note higher pH correspond to lower CD_{50} values.

ANIMALS: Mice, albino, M, 20-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Data reported:
CD_{50}- 560 mg/kg I.P., 1880 mg/kg P.O.
LD_{50}- 610 mg/kg I.P., 1880 mg/kg P.O.

ROUTE AND SITE: I.P. and P.O.

CONTROL INFORMATION: Saline or other parameter

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology

263

COMPOUND: Imidazole, 1-methyl-

000616477

REFERENCE: Nishie, K., Waisa, A.C., and Keyl, A.C.
Tox. Appl. Pharm. 41:301-307, 1969.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, varying degrees of tremor, opisthotonus and tonic extensor seizures. Authors note higher pH correspond to lower CD_{50} values.

ANIMALS: Mice, albino, M, 20-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Data reported:
CD_{50} - 380 mg/kg I.P., 1400 mg/kg P.O.
LD_{50} - 380 mg/kg I.P., 1400 mg/kg P.O.

ROUTE AND SITE: I.P., P.O.

CONTROL INFORMATION: Saline or other parameter

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology.

264

COMPOUND: Imidazole, 2-methyl-

000693981

REFERENCE: Nishie, K., Waiss, A.C. and Keyl, A.C.
Tox. Appl. Pharm. 41:301-307, 1969.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, varying degrees of tremor, opisthotonus and tonic extensor seizures. Authors note higher pH correspond to lower CD_{50} values.

ANIMALS: Mice, albino, M, 20-25 g

PREPARATION AND DOSE or HISTORY OF PATIENT: Data reported:
CD_{50} - 500 mg/kg I.P., 1300 mg/kg P.O.
LD_{50} - 480 mg/kg I.P., 1400 mg/kg P.O.

ROUTE AND SITE: I.P. and P.O.

CONTROL INFORMATION: Saline or other parameter.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology.

COMPOUND: Imidazole, 4-methyl-

000822366

REFERENCE: Nishie, K., Waiss, A.C., and Keyl, A.C.
Tox. Appl. Pharm. 41:301-307, 1969.

OBSERVED NEUROTOXIC EFFECTS: (1) Produced convulsions, tremors, opisthotonus and tonic extensor seizure. Authors report that high pH values correspond to lower CD_{50} values. (2) Tremors at dosages of 100 mg/kg to opisthotonus, terminal tonic extensor seizures at dosages of 150 mg/kg. (3) Produced convulsions.

ANIMALS: (1) Mice, albino, M, 20-25 g.
(2) Chicks, 10 day old
(3) Rabbits, 2.3-3 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Data reported:
(1) LD_{50} - 165 mg/kg I.P., 370 mg/kg P.O.
CD_{50} - 155 mg/kg I.P., 360 mg/kg P.O.
(2) LD_{50} - 210 mg/kg I.P., 174 mg/kg P.O.
(3) 50 - 180 mg/kg I.P. for anticonvulsant testing

ROUTE AND SITE: (1) I.P., P.O. (2) I.P., P.O. (3) I.P.

CONTROL INFORMATION: Saline or other parameter

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology

COMPOUND: 2-Imidazoline-2-bentyl-hydrochloride

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 27 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

265<

COMPOUND: 1H -Indazole, 1-benzyl-3(3-(dimethylamino)propoxy)-

000642728

REFERENCE: Silvestrini, B., Barcellona, P.S., Gabau, A. and Catanese, B.
Tox. Appl. Pharm. 10:148-159, 1967.

OBSERVED NEUROTOXIC EFFECTS: Therapeutic effects of muscle relaxation and sedation at 0.7-1 mg/kg in man. Ataxia and convulsions in mice, rats, rabbits, cats near LD_{50} levels (33 mg/kg I.V. to >1000 mg/kg orally); dogs vomited at lower dosages.

ANIMALS: (1) Mice and Rats
(2) Mice, rats, rabbits, cats, dogs

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: Mouse LD_{50} - 33 mg/kg for I.V., 110 mg/kg for I.P., 218 mg/kg for S.C., and 515 mg/kg for oral. Rat LD_{50} - 100 mg/kg for I.P., 1050 mg/kg for oral.
(2) General effects (convulsions, incoordination):
Mouse: 100 mg/kg I.P., 400 mg/kg oral.
Rat: 50 mg/kg I.P., 400-800 mg/kg oral.
Rabbit: 5 mg/kg I.V.
Cat: 25-50 mg/kg I.P.
Dog: 50 mg/kg oral.

ROUTE AND SITE: Diet, oral dosage, gavage, I.P., I.V.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Varied

EXAM. TYPE: Clinical, pathological, immunological, reproductive.

266

COMPOUND: Indole, 3-(2-aminobutyl)-, monoacetate

000118683

REFERENCE: Gray, J.E., McWade, D.H., Johnston, R.L., Larson, E.J. and Freyburger, W.A. Tox. Appl. Pharm. 4:547-560, 1962.

OBSERVED NEUROTOXIC EFFECTS: Stimulated central nervous system of dogs when dose is greater than 100 mg/kg. LD_{50} value in mice following intraperitoneal administration is 72 mg/kg and 49 mg/kg orally in rats.

ANIMALS: Rats, S-D and Wistar, M and F.
Mice
Dogs, beagle
Rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: Acute, subacute and reproductive studies various levels and schedules.

ROUTE AND SITE: Oral, gavage, I.P., I.M.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry, physiology

COMPOUND: Indole, 3-(2-aminoethyl)-5,6-dihydroxy-

REFERENCE: Baumgarten, H.G., Evetts, K.D., Holman, R.B., Iversen, L.L., Vogt, M. and Wilson, G. and Vogt and Wilson, ibid. 19:1599-1600, 1972. J. Neurochem. 19:1587-1597, 1972.

OBSERVED NEUROTOXIC EFFECTS: Serotonin (5-HT) depleted for several d but normal after 2 mo. Most effect near injection site and in cord; some permanent atrophy of septum and caudate. No loss of norepinephrine, dopamine, or tyrosine hydroxylase activity. 5,6-HT inhibited uptake of 5-HT by brain slices more than of catecholamines Severely toxic doses caused losses of tyrosine hydroxylase and catecholamines.

The second paper gives normal levels of 5-HT and 5-hydroxyindoleacetic acid.

ANIMALS: (1) Rats, Wistar, M and F, 200 g
(2) Rats, Wistar, F, 180-250 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 50 mcg by one of two methods

ROUTE AND SITE: Injected into lateral ventricle

CONTROL INFORMATION: Vehicle given

DURATION OF EXPERIMENT: 68 d

EXAM. TYPE: Biochemistry

COMPOUND: Indole, 3-(2-aminoethyl)-5,6-dihydroxy-

REFERENCE: Baumgarten, H.G., Lachenmayer, L., Bjorklund, A., Nobin, A., and Rosengren, E.
Life Sci. 12(1): 357-364, 1973.

OBSERVED NEUROTOXIC EFFECTS: 5HT in brain and cord depleted for 2 wk, brain 5HT gradually recovered by 2-4 mo., some overshoots in septum hypothamalmus; no recovery within 6 mo in cord. Cited literature to interpret regeneration of serotonin axon lesions by treatment (authors).

ANIMALS: Rats, Wistar AF HAN, M, 180-200 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 75 mcg/rat of free base (creatinine sulfate -H_2O complex) one dose.

ROUTE AND SITE: Inj, lateral ventricle

CONTROL INFORMATION: Age-matched controls

DURATION OF EXPERIMENT: Serial sacr 10 d to 6 mo after injection.

EXAM. TYPE: Biochemical

>267<

COMPOUND: Indole, 3-(2-aminoethyl)-5,6-dihydroxy-

REFERENCE: Richardson, J.S., Cowan,N., Hartman, R. and Jacobowitz, D.M.
Res. Comm. Chem. Path. Pharm. 8(1):29-44, 1974.

OBSERVED NEUROTOXIC EFFECTS: Lowered serotonin; in combination with 6-hydroxydopa lowered norepinephrine and serotonin; no effect on dopamine. Other complex effects reported, and the causes speculated to be selective destruction of noradrenergic and/or serotonergic nerve terminals.

ANIMALS: Rats, S-D, M, 180-220 g, 5-12/group

PREPARATION AND DOSE or HISTORY OF PATIENT: 50 mcg/rat

ROUTE AND SITE: Intraventricular

CONTROL INFORMATION: Vehicle

DURATION OF EXPERIMENT: 14 d

EXAM. TYPE: Behavior

268

COMPOUND: Indole, 3-(2-aminoethyl)-5,7-dihydroxy-

REFERENCE: Baumgarten, H.G., Victor, S.J. and Lovenberg, W.
J. Neurochem. 21:251-253, 1973.

OBSERVED NEUROTOXIC EFFECTS: Progressive depletion of tryptophan hydroxylase in brain and cord. Degeneration of serotonergic neurons. Less potent than 5,6-DDT, but damage apparently greater and more specific. Animals sedated for a few hr but then became hyperactive and pugnacious.

ANIMALS: Rats, Wistar, M, 150-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 150 mcg/rat of free base equivalent in saline and ascorbic acid.

ROUTE AND SITE: Intraventricular

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: 2 and 12 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Indole, 3-(2-aminoethyl)-5-methoxy-

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: Indole, 3-(2-aminoethyl)-6-methoxy-

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

693

COMPOUND: Indole, 3-(2-aminopropyl)-, acetate

REFERENCE: Gray, J.E., McWade, D.H., Johnston, R.L., Larson, E.J. and Freyburger, W.A.
Tox. Appl. Pharm. 4:547-560, 1962.

OBSERVED NEUROTOXIC EFFECTS: Stimulated central nervous system of dogs when dose is greater than 100 mg/kg. Signs of intoxication subsided after second day. LD_{50} value in mice is 38 mg/kg I.P. and 22 mg/kg orally in rats.

ANIMALS: Rats, S-D and Wistar, M and F.
Mice
Dogs, beagle
Rabbits

PREPARATION AND DOSE or HISTORY OF PATIENT: Acute, subacute and reproductive studies various levels and schedules.

ROUTE AND SITE: Oral, gavage, I.P., I.M.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry, physiology

COMPOUND: Indole, 3-(2-(dibutylamino)ethyl)-

REFERENCE: Szara, S.
Biochem. Pharm. 8: 32, 1961.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused disturbances of the autonomic, emotiona perceptual and thinking systems, dependent on the 6-hydroxylation rate in liver; dealkylation, for instance, produced inactive metabolites. Thus diethyl, dimethyl, and dipropyl homologs were active, while dibutyl was barely active, and dihexyl was inactive.

ANIMALS: Human

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 mg/kg

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: ns

COMPOUND: Indole, 3-(2-(diethylamino) ethyl)-

000061518

REFERENCE: Szara, S.
Biochem. Pharm. 8: 32, 1961.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused disturbances of the autonomic, emotional, perceptual and thinking systems, dependent on the 6-hydroxylation rate in liver; dealkylation, for instance, produced inactive metabolites. Thus diethyl, dimethyl, and dipropyl homologs were active, while dibutyl was barely active, and dihexyl was inactive.

ANIMALS: Human

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 mg/kg

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: ns

COMPOUND: Indole, 3-(2-dihexylaminoethyl)-

REFERENCE: Szara, S.
Biochem. Pharm. 8: 32, 1961.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused disturbances of the autonomic, emotional, perceptual and thinking systems, dependent on the 6-hydroxylation rate in liver; dealkylation, for instance, produced inactive metabolites. Thus diethyl, dimethyl, and dipropyl homologs were active, while dibutyl was barely active, and dihexyl was inactive.

ANIMALS: Human

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: ns

T42
A

COMPOUND: Indole, 3-(2-dimethylaminoethyl)-

000061507

REFERENCE: Gallagher, C.H., Koch, J.H. and Hoffman, H.
Int. J. Neuropharmacol. 6: 223-228, 1967.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, spasms. The authors showed that the convulsions originated in the brain and that the spasms originated in the spinal cord.

ANIMALS: Sheep, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Dimethyl tryptamine (1) and 5-methoxydimethyltryptamine (2) were administered as HCl derivatives; 5-hydroxydimethyltryptamine (3) as a bioxalate derivative. 0.05-0.1 mg/kg of each, mixed, or 0.05-0.1 mg/kg of (2), or 0.25-0.5 mg/kg of (3) were equivalent doses. One sheep that was poisoned while grazing was obtained.

ROUTE AND SITE: I.V., jugular; oral.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, pharmacology

212

COMPOUND: Indole, 3-(2-dimethylaminoethyl)-

000061507

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE
or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: Indole, 3-(2-dimethylaminoethyl)-

000061507

REFERENCE: Szara, S.
Biochem. Pharm. 8: 32, 1961.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused disturbances of the autonomic, emotional, perceptual and thinking systems, dependent on the 6-hydroxylation rate in liver; dealkylation, for instance, produced inactive metabolites. Thus diethyl, dimethyl, and dipropyl homologs were active, while dibutyl was barely active, and dihexyl was inactive.

ANIMALS: Human

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 mg/kg

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: ns

COMPOUND: Indole, 3-(2-(dimethylamino)ethyl)-5-methoxy-
(5-methoxydimethyltryptamine)

REFERENCE: Callagner, C.H., Koch, J.H. and Hoffman, H.
Int. J. Neuropharmacol. 6: 223-228, 1967.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, spasms. The authors showed that the convulsions originated in the brain and that the spasms originated in the spinal cord.

ANIMALS: Sheep, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Dimethyl tryptamine (1) and 5-methoxydimethyltryptamine (2) were administered as HCl derivatives; 5-hydroxydimethyltryptamine (3) as a bioxalate derivative. 0.05-0.1 mg/kg of each, mixed, or 0.05-0.1 mg/kg of (2), or 0.25-0.5 mg/kg of (3) were equivalent doses. One sheep that was poisoned while grazing was obtained.

ROUTE AND SITE: I.V., jugular; oral.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, pharmacology

2273

COMPOUND: Indole, 3-(2-dipropyl amino)ethyl)-

000061529

REFERENCE: Szara, S.
Biochem. Pharm. 8: 32, 1961.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused disturbances of the autonomic, emotional, perceptual and thinking systems, dependent on the 6-hydroxylation rate in liver; dealkylation, for instance, produced inactive metabolites. Thus diethyl, dimethyl, and dipropyl homologs were active, while dibutyl was barely active, and dihexyl was inactive.

ANIMALS: Human

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg

ROUTE AND SITE: ns

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: ns

274

COMPOUND: Indol-5-ol-3-02-(dimethylamino)ethylo-

0000487934

REFERENCE: Gallagher, C.H., Koch, J.H. and Hoffman, H.
Int. J. Neuropharmacol. 6: 223-228, 1967.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, spasms. The authors showed that the convulsions originated in the brain and that the spasms originated in the spinal cord.

ANIMALS: Sheep, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Dimethyl tryptamine (1) and 5-methoxydimethyltryptamine (2) were administered as HCl derivatives; 5-hydroxydimethyltryptamine (3) as a bioxalate derivative. 0.05-0.1 mg/kg of each, mixed, or 0.05-0.1 mg/kg of (2), or 0.25-0.5 mg/kg of (3) were equivalent doses. One sheep that was poisoned while grazing was obtained.

ROUTE AND SITE: I.V., jugular; oral.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, pharmacology

COMPOUND: Indol-4-ol, 3(2-(dimethyl amino)ethyl)- (Psylocin)

000520536

REFERENCE: Horita, A. and Weber, L.J.
Tox. Appl. Pharm. 4: 730-737, 1962.

OBSERVED NEUROTOXIC EFFECTS: After administration of psilocybin, psylocin (4-hydroxy analog of psilocybin) appeared in tissues including brain, brain peak 25-30 min after dose. Piloerection, exophthalmos, motor incoordination followed brain levels of psylocin. Pretreatment with β-glycerophosphate did not alter distribution of psylocin nor behavior. Interpreted to mean that psilocybin was rapidly dephosphorylated, and central nervous system effects exerted by the psylocin metabolite.

ANIMALS: Mice, albino, 25-35g, 6/group

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg/kg, equalling 0.35 mmole/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: "Normal mice", details ns

DURATION OF EXPERIMENT: Serial to 30 min

EXAM. TYPE: Biochemistry, behavior

COMPOUND: Indol-4-ol, 3-(2-(dimethylamino)ethyl)-, dihydrogen phosphate (Psilocybin)
000520525

REFERENCE: Horita, A. and Weber, L.J.
Tox. Appl. Pharm. 4: 730-737, 1962.

OBSERVED NEUROTOXIC EFFECTS: After administration of psilocybin, psylocin (4-hydroxy analog of psilocybin) appeared in tissues including brain, brain peak 25-30 min after dose. Piloerection, exophthalmos, motor incoordination followed brain levels of psylocin. Pretreatment with β-glycerophosphate did not alter distribution of psylocin nor behavior. Interpreted to mean that psilocybin was rapidly dephosphorylated, and central nervous system effects exerted by the psylocin metabolite.

ANIMALS: Mice, albino, 25-35g, 6/group

PREPARATION AND DOSE
or HISTORY OF PATIENT: 72 mg/kg, equalling 0.35 mmole/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: "Normal mice", details ns

DURATION OF EXPERIMENT: Serial to 30 min

EXAM. TYPE: Biochemistry, behavior

2752

COMPOUND: Indol-4-ol, 3-(2-(dimethylamino)ethyl)-, dihydrogen phosphate
000520525

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced excitement, abnormal postures, abnormal EEGs, then depression.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1-50 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

>9/2 276<

COMPOUND: Isocyanic acid, p-bromophenyl ester

REFERENCE: Lessel, B. and Towlerton, R.G.
Fd. Cosmet. Toxicol. 5:741-743, 196 .

OBSERVED NEUROTOXIC EFFECTS: Swaying gait, ataxia, weak hindlimbs, and swelling-degeneration of the axons. Demyelination of spinal cord. Neuronal degeneration. Death. Spinal cord lesions.

ANIMALS: 16 Lambs, 8 wk, 19-24 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 150-200 mg/kg/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Sacr.

EXAM. TYPE: Dissection

COMPOUND: Isoglutamine, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Isonicotinic acid, 2-(2-(benzylcarbam.yl)ethyl)hydrazide

000051127

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 9 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Alder, S. and Zbinden, G.
Agents and Actions 3/4: 233-243, 1973.

OBSERVED NEUROTOXIC EFFECTS: Water intake increased at weekends (no dose given), normal during treatment. In Hot Plate Test, delayed response; in Foot Print Test, gait not altered; in Rotating Rod Test performance impaired in some rats. All rats had peripheral neuropathy after 3 d, all doses: degenerative changes, especially of myelin. Brain and cord no changes. Thymus moderate atrophy with 600 mg/kg.

ANIMALS: Rats, CFH Zu, F. 38-53g, 6 groups of 8-10 each.

PREPARATION AND DOSE or HISTORY OF PATIENT: 200, 400, 600 mg/kg, 5d/wk, for 5-26 doses.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 6 groups given water orally.

DURATION OF EXPERIMENT: Serial sacr 1-5 wk.

EXAM. TYPE: Behavior, histology

>818

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Botta, J.A., Jr. and Carlton, W.W.
Tox. Appl. Pharm. 11:35-48, 1967.

OBSERVED NEUROTOXIC EFFECTS: Excitement, ataxia, convulsions; cerebellar lesions. Dose-relationships with symptoms and pathology are explored.

ANIMALS: Drakes, Pekin and Rouen, 30-36 hr old

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-0.3% in diet; 40-1250 mg/kg/d i.p. 7 d; 0.001-0.1% in diet.

ROUTE AND SITE: Oral, I.P.

CONTROL INFORMATION: Untreated

DURATION OF EXPERIMENT: Up to 3 mo. or more.

EXAM. TYPE: Mortality, behavior, pathology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Carlton, W.W. and Kreutzberg, G.
Am. J. Path. 48:91-98, 1966.

OBSERVED NEUROTOXIC EFFECTS: Tremors, ataxia. Spongy degeneration (vacuoles, demyelination) in cerebellar white matter, also in optic lobe, hemispheres, cord. Local axonal degeneration, proliferation of glia, edema of astrocytes. No protection from pyridoxal.

ANIMALS: Drakes, Pekin, day-old, 4 grps of 10, 3 grps treated.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 g/kg in diet with 0, 0.2, 1 g/kg of pyridoxal hydrochloride.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 1 group untreated.

DURATION OF EXPERIMENT: 4 wk.

EXAM. TYPE: Behavior, histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Carlton, W.W.
Avian Dis. 11:241-254, 1967.

OBSERVED NEUROTOXIC EFFECTS: Neuropathy (taxia, tremor, convulsions) severe only with 0.15 and 0.30% feeding. Central Nervous System spongy degeneration especially in cerebellar medulla, less in medulla oblongata, optic lobes and cord. No protection if 0.2% pyridoxine was fed. Growth depressed in all, mortality 25-85% dose-related.

ANIMALS: Chicks: broiler stock, M, day-old, grps of 20.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.05-0.30% of diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Diet only

DURATION OF EXPERIMENT: 8 wk

EXAM. TYPE: Behavior, histology

278

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Cavanagh, J.B.
J. Neurol. Neurosurg. Psychiat. 30:26-33, 1967.

OBSERVED NEUROTOXIC EFFECTS: Weakness and wasting of hindlimb muscles, varying degrees. Denervation of mainly motor, also sensory nerves in distal muscles, medium sized fibers specially. Pattern like that in acute intermittent porphyria in man, unlike that from organophosphourses.

ANIMALS: Rats, Wistar, M, 270-300 g (12), av. 68 g (12), av. 73 g (8).

PREPARATION AND DOSE
or HISTORY OF PATIENT: 250 mg/kg/d in diet or in two doses s.c.

ROUTE AND SITE: Oral or s.c.

CONTROL INFORMATION: None reported

DURATION OF EXPERIMENT: Serial sacr to 12 wk

EXAM. TYPE: Behavior, histology

260

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Gammon, G.D., Burge, F.W. and King, G.
Arch. Neurol. Psychiat. 70:64-69, 1953.

OBSERVED NEUROTOXIC EFFECTS: Signs of peripheral neuropathy, regressed on stopping the drug. Inducing dose 4.5-13.5 mg/kg, "in the range in which toxicity is to be excepted."

ANIMALS: Human: 14 cases selected from 46 "with similar complaints" in a series of 408 treated with isoniazid.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 300-700 mg/d, duration ns.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Hildebrand, J., Joffroy, A. and Coers, C.
Arch. Neurol. 19:60-70, 1968.

OBSERVED NEUROTOXIC EFFECTS: At 3 d, 10% of sciatic nerve fibers damaged and conduction reduced; at 7 d myelin disruped in 32% of fibers, axonal fragmentation, collateral sprouting of subterminal fibers, altered muscle action potentials; at 13 d 76% of fibers damaged, slower motor condution, large group atrophy of muscles. After 37 d of no treatment much nerve damage persisted, no recovery of muscles. Collateral branching explained continued motor activity.

ANIMALS: 19 Rats, S-D, M, Age 3 mo. 260-300 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 90 mg/rat/d, 3-13 d

ROUTE AND SITE: I.G.

CONTROL INFORMATION: 23 Matched rats, 280-320 g

DURATION OF EXPERIMENT: Sacr after 4-50 d observation

EXAM. TYPE: Electrophysiology, histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.1 mM/kgm

ROUTE AND SITE: I.P., I.V.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

1582

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Jones, W.A. and Jones, G.P.
Lancet:1073-1074, 1953.

OBSERVED NEUROTOXIC EFFECTS: Polyneuropathy of limbs, resembling pellagra and attributed to competitive inhibition of nicotinic acid and perhaps other B-vitamins by the drug.

ANIMALS: Human: 2 case-reports, M aged 23 and F aged 18

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 300 mg/d (5 mg/kg/d) for over 6 wk, admitted to hospital 4 wk after treatment ended.
(2) 450 mg/d (12 mg/kg/d) for 3 mo., repeated after 4 mo. interval, admitted 2 wk later.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: (1) 1 mo. observation, (2) 3 wk.

EXAM. TYPE: Clinical

282

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Noel, P.R.B., Worden, A.N. and Palmer, A.C.
Tox. Appl. Pharm. 10:183-198, 1967.

OBSERVED NEUROTOXIC EFFECTS: No constant evidence of peripheral nervous system damage. Brain damage mainly due to subcortical myelin of hemispheres, considered edematous.

ANIMALS: 12 Dogs, Pembroke Corgi, 6M, 6F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 25 or 50 mg/kg/d in gelatin capsules, 6d/wk. High dose reduced to 40 mg/kg due to convulsions, and then both groups reduced to 5 or 25 mg. Continued treatment resulted in death, so 25 mg/kg reduced to 15 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 6 undosed controls.

DURATION OF EXPERIMENT: 195 d

EXAM. TYPE: Clinical, biochemistry, autopsy

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Ochoa, J.
Brain 93:831-850, 1970.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy; sural nerves myelinated and unmyelinated fibers were damaged, with differences; regeneration and degeneration of regenerated fibers were seen.

ANIMALS: 9 Humans, M and F, aged 35-70 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 300-500 mg/d; 1 patient given 2 g/d for 5 d in error.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to about 3 yr.

EXAM. TYPE: Clinical and lab, histology (biopsy)

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Palmer, A.C. and Noel, P.R.B.
Nature 205:506-507, 1965.

OBSERVED NEUROTOXIC EFFECTS: Seperation of fibers in subcortical myelin, ballooning, but axons intact, activation of microglia and hypertrophy of astrocytes.

ANIMALS: Dogs

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 or 15 mg/kg/d for up to 6 mo.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Control dogs, no details.

DURATION OF EXPERIMENT: Up to 6 mo.

EXAM. TYPE: Histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Ramakrishna, T. and Smith, B.H.
Neurology 20:1142-1145, 1970.

OBSERVED NEUROTOXIC EFFECTS: Generalized convulsions, abnormal EEG.

ANIMALS: Human: 2 case-reports (F, 14 yr; F, 22 yr)

PREPARATION AND DOSE or HISTORY OF PATIENT: Two attempted suicides: 2.4 g and about 5 g, single doses (50 and 93 mg/kg)

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, EEG

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Schlaepfer, W.W. and Hager, H.
Am. J. Path. 45:209-216, 1964.

OBSERVED NEUROTOXIC EFFECTS: Primary axonal degeneration with swelled mitochondria in peripheral nerves; changes in axoplasm.

ANIMALS: 20 rats, S-D, F, 250-400 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 250 mg/kg/d for 6-16 d.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: "Normal rats" number and treatment ns.

DURATION OF EXPERIMENT: Serial sacr to 16 d

EXAM. TYPE: Histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Schlaepfer, W.W. and Hager, H.
Am. J. Path. 45:423-430, 1964.

OBSERVED NEUROTOXIC EFFECTS: Specific report on breakdown of myelin. Collapse of cylinder, myelin globules formed within Schwann cell cytoplasm with reactive changes and phagosome-like vacuoles; products transferred to macrophages.

ANIMALS: 20 rats, S-D, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 350 mg/kg/d for 6-16 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 "normal rats" as control.

DURATION OF EXPERIMENT: Serial sacr to 154 d.

EXAM. TYPE: Histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Schlaepfer, W.W. and Hager, H.
Am. J. Path. 45:679-686, 1964.

OBSERVED NEUROTOXIC EFFECTS: Focal disruption of axons and myelin sheaths. Regeneration studied: mild fibrosis of endoneurium, shcwann-cell proliferation, regeneration of axons interacting with schwann-cell processes and remyelination.

ANIMALS: 20 rats, S-D, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 350 mg/kg/d for 6-15 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 "Normal rats" as control.

DURATION OF EXPERIMENT: Serial sacr to 154 d

EXAM. TYPE: Histology

285

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Sea, C.P. and Peterson, R.G.
Exp. Neurol. 48:.252-260, 1975.

OBSERVED NEUROTOXIC EFFECTS: Portions of both sciatic nerves (one for histology, the other for biochemistry): neuropathy varied axon to axon and rat to rat. Degeneration of myelin; Schwann cells appeared to transform into macrophages. Loss of the main protein band (electrophoresis).

ANIMALS: 30 Rats, S-D, M, 200-300 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 270 mg/kg/d till hyperactivity seen (usually 6 d), then 200 mg/kg/d to day 14.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 2 Controls, saline treated.

DURATION OF EXPERIMENT: Serial sacr to 14 d

EXAM. TYPE: Histology, biochemistry

286

COMPOUND: Isonicotinic acid, hydrazide

000054855

REFERENCE: Smith, B.
J. Neurol. Neurosurg. Psychiat. 30: 506-510, 1967.

OBSERVED NEUROTOXIC EFFECTS: The myenteric plexus was examined, and histological changes were found. The author suggests her method for screening for neurotoxicity by looking for damage to the myenteric plexus in the large intestine.

ANIMALS: 45 Mice, TO, CFW and Porton strains, 20-25 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5 mg twice weekly for 5-20 doses, 9 mice
Acute study: 10 mg I.P. or 2 mg I.V. one dose

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 2 d to 3 mo after last dose. Acute: 20 min.

EXAM. TYPE: Histology

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Terman, D.S. and Teitelbaum, D.T.
Neurology 20:299-304, 1970.

OBSERVED NEUROTOXIC EFFECTS: Intractable convulsions, metabolic acidosis. All recovered eventually.

ANIMALS: Human: 4 cases (M, 35; M, 21; F, 16; F, 20)

PREPARATION AND DOSE
or HISTORY OF PATIENT: Single doses: (1) amt unknown, (2) 30 g, (3) approx 10 g plus pyridoxine, (4) amt unknown. In each case self-administered, thought to be over 7 g.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, hospital lab.

COMPOUND: Isonicotinic acid, hydrazide

000054853

REFERENCE: Tomkin, G.H.
Practitioner 211:773-777, 1973.

OBSERVED NEUROTOXIC EFFECTS: Loss of strength in arms and legs, absent tendon reflexes, plantar responses flexor, impaired sensation to pinpricks. Complication: sideroblastic anemia. After all drugs were discontinued and blood and pyridoxine given, patient began recovery. In 3 wk patient walked unaided, in 4 mo. sensations and tendon reflexes except ankle-jerk were normal.

ANIMALS: 1 Human, M, aged 67 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dose 300 mg/d as antituberculosis therapy, after 2 yr complained of limb numbness; was found unable to walk unaided.

ROUTE AND SITE: ns.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 2 yr of drug therapy, follow up.

EXAM. TYPE: Hospital

>87<

COMPOUND: Isonicotinic acid 2-isopropyl hydrazide phosphate

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 200 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

288

COMPOUND: Isonicotinic acid, 2-(sulfomethyl)hydrazide, sodium salt

003804895

REFERENCE: Noel, P.R.B., Worden, A.N. and Palmer, A.C.
Tox. Appl. Pharm. 10:183-198, 1967.

OBSERVED NEUROTOXIC EFFECTS: No constant evidence of peripheral nervous system damage. Brain damage mainly due to subcortical myelin of hemispheres, considered edematous.

ANIMALS: 18 Dogs, Pembroke Corgi, 9 M, 9 F

PREPARATION AND DOSE or HISTORY OF PATIENT: 6, 30 or 60 mg/kg/d in gelatin capsules, 6d/wk. High dose reduced to 48 mg/kg due to convulsions, and then to 40 mg/kg. Deaths caused further reduction to 20 or 10 mg/kg/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 6 undosed controls.

DURATION OF EXPERIMENT: 195 d

EXAM. TYPE: Clinical, biochemistry, autopsy

COMPOUND: Isonicotinic acid, 2-(sulfomethyl) hydrazide, sodium salt

003804895

REFERENCE: Palmer, A.C. and Noel, P.R.B.
Nature 205:506-507, 1965.

OBSERVED NEUROTOXIC EFFECTS: Seperation of fibers in subcortical myelin, ballooning, but axons intact, activation of microglia and hypertrophy of astrocytes. Severe laminar necrosis of cerebral cortex.

ANIMALS: Dogs

PREPARATION AND DOSE or HISTORY OF PATIENT: 6, 10, or 20 mg/kg/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Control dogs, no details

DURATION OF EXPERIMENT: Up to 6 mo.

EXAM. TYPE: Histology

COMPOUND: Lactic acid, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 9.6 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

289

COMPOUND: Lead

007439921

REFERENCE: Anku, V.D. and Harris, J.W.
J. of Pediatrics 85(3):337-340, 1974.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neuropathy, fatigue, headache, epistaxis, clumsiness and limb weakness.

ANIMALS: 1 Human, M, 6 yrs.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Ingestion of lead-base paint chips.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 5 mo.

EXAM. TYPE: Clinical, hematology.

290

COMPOUND: Lead

007439921

REFERENCE: Baloh, R., Sturm, R., Green, B. and Glaser, G.
Arch. Neurol. 32:326-330, 1975.

OBSERVED NEUROTOXIC EFFECTS: All subjects asymptomatic when evaluated. Hyperactivity correlated with increased lead levels, but quantitative tests did not. Authors comment about "uncontrolled variables."

ANIMALS: Human children aged over 3 1/2 yr with 2 blood tests over 50 mcg/Pb/100 m

PREPARATION AND DOSE or HISTORY OF PATIENT: History, physical exam, blood Pb determination, and psychological tests (motor, perceptual-motor, verbal-cognitive, memory, quantitative).

ROUTE AND SITE: N/A

CONTROL INFORMATION: Controls matched from files (m of age, sex, race, background) and screened at under 30 mcg Pb/100 ml blood.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: History, physical, hematological, behavioral

COMPOUND: Lead

007439921

REFERENCE: Beattie, A.D., Briggs, J.D., Canavan, J.S.F., Doyle, D., Mullin, P.J. and Watson, A.A.
Quart. J. Med. 44(174): 275-284, 1975.

OBSERVED NEUROTOXIC EFFECTS: Two of the cases showed severe neuropathy characterized by sudden flaccid paralysis 15 days after the dose, with quadriplegia and respiratory paralysis. Peripheral nervous system motor end plates lacked innervation and showed degenerated axons and myelin.

ANIMALS: Human: 5 cases, all associated

PREPARATION AND DOSE or HISTORY OF PATIENT: Self-administration of lead-opium pills obtained by burglary, ground, suspended, and injected (3-?12 pills) one dose.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Absent

DURATION OF EXPERIMENT: About 2 wk

EXAM. TYPE: Clinical, biochemistry, histology (autopsy)

COMPOUND: Lead

007439921

REFERENCE: Carson, T.L., Van Gelder, G.A., Karns, G.C. and Buck, W.B.
Arch. Env. Hlth. 29:154-156, 1974.

OBSERVED NEUROTOXIC EFFECTS: Blood lead of controls 4.7, lows 18.6, highs 34.8 mcg/100 ml; of lambs at 2-4 wk of age controls 6.0, lows 17.0, highs 25.0 mcg/100 ml; of lambs at 10-12 wk controls 4.0, lows 9.0, highs 14.0 mcg/100 ml. Rate of learning six visual discrimination problems: highs but not lows significantly slower than controls.

ANIMALS: Lambs born to ewes fed high or low lead diets:
7 in high group, 8 in low group.
Used eventually: 4 control, 8 low, and 6 high lambs.

PREPARATION AND DOSE or HISTORY OF PATIENT: High: dams fed 4.5 mg/kg/d.
Low: dams fed 2.3 mg/kg/d.
Lambs weaned at 3 mo. exposure ceased.

ROUTE AND SITE: Diet

CONTROL INFORMATION: Lambs from ewes fed normal diet: 9 lambs.

DURATION OF EXPERIMENT: About 15 mo.

EXAM. TYPE: Behavioral, blood chemistry

291A

COMPOUND: Lead

007439921

REFERENCE: David, O.J.
Lancet i, 866, 1974.

OBSERVED NEUROTOXIC EFFECTS: Criticisms of paper by Lansdown et al., Lancet i, 538, 1974. (1) Blood lead does not signify lead burden, without lead mobilization tests. (2) Behaviorial controls should be outside the affected area, and methods should be justified for purpose (lead-free population, and scale intended to measure hyperkinesis). (3) Sex imbalance in expected frequencies of behavior disturbance (boys more than girls) should be considered in selecting the study sample and in data-processing; same with age-imbalance (omission of cases under 6 yr old). Therefore, conclusions are not proved by data (may still be correct, but issue unresolved).

ANIMALS: Humans

PREPARATION AND DOSE or HISTORY OF PATIENT: Industrial exposure to emissions from a lead smelter

ROUTE AND SITE: ns.

CONTROL INFORMATION: Subject of argument

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Subject of argument

292

COMPOUND: Lead

007439921

REFERENCE: Krigman, M.R.
Env. Hlth. Persp. 4:98, 1973. (Abstracts).

OBSERVED NEUROTOXIC EFFECTS: Thinner cortical mantle, smaller neurons, less developed neuropil, fewer synapses but larger. Lead retarded neuronal growth but not maturation, whereas undernourishment affected both growth and maturation.

ANIMALS: Rats, Long-Evans, age 30 d.

PREPARATION AND DOSE or HISTORY OF PATIENT: Amt ns., to undernourished litters.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology

COMPOUND: Lead

007439921

REFERENCE: Lansdown, R.G., Shepherd, J., Clayton, B.E., Delves, H.T., Graham, P.J. and Turner, W.C.
Lancet 1:538-541, 1974.

OBSERVED NEUROTOXIC EFFECTS: Weak positive correlation of blood lead with distance of home from source of pollution. No relationship between blood lead and level of mental functioning by any of several measurements (dysfunction was found to be related to social factors).

ANIMALS: Human: whole population under 17 in working-class area, 317; 275 of these available for testing, 232 (84%) were tested, 215 (78%) had blood tests, 227 (82%) were behavior-rated, social-worker data were obtained on 218 (79%); 1% did not take part (parents refused).

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to airborne emissions and dust from a smelting factory for whole life, gauged by distance of home from source in steps of 100 m from 0-500 and 500+.

ROUTE AND SITE: Inhalation of airborne emissions and of dusts in homes and on roads, ingestion of dusts.

CONTROL INFORMATION: Another, non-exposed, population

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, blood chemistry

COMPOUND: Lead

007439921

REFERENCE: Moore, J.F., Mushak, P. and Krigman, M.R.
Env. Hlth. Persp. 10:266, 1975 (Abstract).

OBSERVED NEUROTOXIC EFFECTS: Level of lead in cerebrum increased just before onset of convulsions, in nuclei and mitochondria more than in other organelles.

ANIMALS: Guinea-pigs

PREPARATION AND DOSE or HISTORY OF PATIENT: "large doses"

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 5 d

EXAM. TYPE: Biochemistry

COMPOUND: Lead

007439921

REFERENCE: O'Tuama, L.A., Howard, J.L., Kim, C.S. Mushak, P.M. and Krigman, M.R.
Env. Hlth. Persp. 10:266, 1975 (Abstract).

OBSERVED NEUROTOXIC EFFECTS: At 5 min lead was strongly concentrated in choroid plexus and meninges; low concentration in brain; ouabain reduced choroid plexus level to 2%, meninges to 13%, brain to 70% of controls. At 240 min these tissue-to-blood ratios had fallen and ouabain had no effect. Interpreted in terms of lead transport and its importance in lead encephalopathy.

ANIMALS: Guinea-pigs

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.01 mcCi/kg with/without ouabain

ROUTE AND SITE: ns.

CONTROL INFORMATION: Lead regarded as control

DURATION OF EXPERIMENT: 240 min

EXAM. TYPE: Biochemistry

293>

<294>

COMPOUND: Lead

007439921

REFERENCE: Popoff, N., Weinberg, S. and Feigin, I.
Neurology 13:101-114, 1963.

OBSERVED NEUROTOXIC EFFECTS: Clinically: vomiting, headache, stupor, papilledema, coma, convulsions. Edema of brain, petechial hemorrhages in cortex, demyelination and astrocytic and microglial reactions. Authors concluded that vascular damage contributed to the encephalopathy.

ANIMALS: Human: 6 cases aged 1 1/2-3

PREPARATION AND DOSE or HISTORY OF PATIENT: History of eating paint for 4-6 mo.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 5 died in 9 hr to 8 d of hospitalization, one lived 39 d

EXAM. TYPE: Autopsy, histology

COMPOUND: Lead

007439921

REFERENCE: Pueschel, S.M.
Env. Hlth. Persp. 7:13-16, 1974.

OBSERVED NEUROTOXIC EFFECTS: 23-27% found to have neurological dysfunction and motor impairment; assessed as low average mental abilities at first examination, some improvement reported at reexamination 1 1/2 - 3 yr later.

ANIMALS: Human: 58 children diagnosed as lead-poisoned in a survey of 705 children in Boston. Analysis of hair, then blood.

PREPARATION AND DOSE or HISTORY OF PATIENT: Evaluation, then reexamination 1 1/2 - 3 yr later.

ROUTE AND SITE: ns.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, behavior

COMPOUND: Lead

007439921

REFERENCE: Roberts, T.M., Hutchinson, T.C., Paciga, J., Chattopadhyayt, A., Jervis, R.E. and Van Loon, J.
Science 186:1120-1123, 1974.

OBSERVED NEUROTOXIC EFFECTS: 2 cases of neuropathy, 3 of slow nerve conduction; increased absorption not enough to cause clear-cut symptoms but "may cause metabolic and subtle neurological changes, "found in 10-15% of 21 selected children with excessive lead loads.

ANIMALS: Humans: 286 residents of zone contaminated by lead smelter A, 1425 close to smelter B.

PREPARATION AND DOSE or HISTORY OF PATIENT: Emissions estimated from A: 15,000 kg/yr, from B: 30,000 kg/yr. Soil near A contained 40 mg lead/g, soil near B contained 16 mg/g. More dust than fumes. Blood lead levels near source A: 27 mcg/100 ml, near B: 28 mcg/100 ml, but levels over 40 occured in <1% of controls, in 28% near source A (summer) and 13% near source B (winter).

ROUTE AND SITE: Inhalation, skin contact, ingestion

CONTROL INFORMATION: 1232 socioeconomically matched urbanites not exposed. Urban control soil content 0.1-0.5 mg/g. Mean blood lead level of control children was 19 mcg/100 ml.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, biochemistry

COMPOUND: Lead

007439921

REFERENCE: Rosenblaum, W.I.
Acta Neuropathologica. 5:54-60, 1965.

OBSERVED NEUROTOXIC EFFECTS: Lead caused dilation of pial arteries and inhibited the contractile response to barium. At lower doses, the responses were reversible, but at concentrations of 2% or higher the arteries never regained their responsiveness to barium.

ANIMALS: Mice, Swiss-Webster, Male, 20 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.0 mg/100 g

ROUTE AND SITE: Injection

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Dissection

295

296

COMPOUND: Lead

007439921

REFERENCE: Sachs, H.K.
Env. Hlth. Persp. 7:41-45, 1974.

OBSERVED NEUROTOXIC EFFECTS: Symptoms found in 12.2% of subjects in year 1, falling to 4.2% in year 5 of study: drowsiness, vomiting, irritability, g-i, behavior, ataxia, convulsions, stupor peripheral neuropathy; only one death.

ANIMALS: Human: 6804 (3.2%) of 213,598 screened who had ≥50 mcg/100 ml of blood, in Chicago.

PREPARATION AND DOSE or HISTORY OF PATIENT: History of eating paint or plaster 80%, x-ray finding of paint chips in abdomen in another 10%.

ROUTE AND SITE: Oral mainly

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Several yr.

EXAM. TYPE: Clinical, blood chemistry

COMPOUND: Lead

007439921

REFERENCE: SeppHlHinen, A.M., Tola, S., Hernberg, S. and Kock, B.
Arch. Env. Hlth. 30:180-183, 1975.

OBSERVED NEUROTOXIC EFFECTS: Blood lead regularly monitored and never above 70 mcg/100 ml (accepted safety norm). Yet nerve-conduction in selected muscles was slower (P<0.001) than in controls. As no complaints were involved, authors term findings "subclinical neuropathy" and suggest that safety norms be reconsidered.

ANIMALS: Human: 26 workers (18 M, 8 F) at a battery factory in Finland.

PREPARATION AND DOSE or HISTORY OF PATIENT: No previous exposure, current exposures (4.6 yr range 13 mo.-17 yr. slight or moderate. Clinical exam. and electromyography

ROUTE AND SITE: Occupational exposure, inhalation.

CONTROL INFORMATION: Age-sex-matched data from normals (blue-collar) assembled at Inst. Occupational Hlth., Helesinki, about 200; Blood lead estimated 10-13 mcg/100 ml.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

COMPOUND: Lead (Pb^{210})

REFERENCE: Thomas, J.A., Dallenbach, F.D. and Thomas, M.
J. Path. 109:45-50, 1973.

OBSERVED NEUROTOXIC EFFECTS: Study to localize lead in developing cerebellum: in cytoplasm of capillary endothelial cells, later in astrocyte foot-processes. After 72 hr lead associated with edema.

ANIMALS: 4 Rats, Wistar, F, each with litter aged 1 d; 2 grps trtd.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 or 10 mcCi.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 2 grps

DURATION OF EXPERIMENT: Serial sacr to 168 hr.

EXAM. TYPE: Autoradiography after histology

2972

COMPOUND: Lead

007439921

REFERENCE: Zaworski, R.E. and Oyasu, R.
Arch. Env. Hlth. 27:383-386, 1973.

OBSERVED NEUROTOXIC EFFECTS: By atomic absorption: 0.5 ± .68 ppm in wet tissue of normals; increase in first two decades of life. 0.34 ± 0.03 ppm in tumor brains, statistically non-significant.

ANIMALS: Humans: Autopsy material (brains) from 4 hospitals, only R frontal lobes studied: 191 normal brains, 9 with tumors.

PREPARATION AND DOSE or HISTORY OF PATIENT: No known industrial exposure to lead, childhood exposure unknown. Samples obtained from ten patient with brain tumors and 191 normals.

ROUTE AND SITE: ns.

CONTROL INFORMATION: 191 Control brains, lead content undetectable to 7.9 ppm

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Chemistry

298

COMPOUND: Lead acetate, trihydrate

REFERENCE: Roy, S., Hirano, A., Kochen, J.A. and Zimmerman, H.M.
Acta Neuropath. 30: 287-294, 1974.

OBSERVED NEUROTOXIC EFFECTS: Attenuated endothelial cells of cerebral vessels with altered ultrastructure.

ANIMALS: Chick eggs

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-75 mcg inj into yolksac on d 4 of incubation.

ROUTE AND SITE: Inj, yolksac

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Living embryos sacrificed serially 5-18 d of incubation.

EXAM. TYPE: Histology.

COMPOUND: Lead, bis (acetato)tetrahydrooxytri
001335326

REFERENCE: Clasen, R.A., Hartmann, J.F., Coogan, P.S., Pandolfi, S., Laing, I. and Decker, R.
Env. Hlth. Persp. 7:175-185, 1974.

OBSERVED NEUROTOXIC EFFECTS: At 6-18 wk onset of ataxia, nystagmus, weakness, convulsions; rise of blood Pb and urinary ALA, fall of Hb. Central nervous system edema of white matter of hemispheres and cerebellum; granular precipitate with expanded extracellular space; axonal swelling in cortex only.

ANIMALS: 4 Rhesus monkeys (3 M, 1 F) age 5-6 mo. newly weaned.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 g with 1000 IU vitamin D in corn oil 3 doses/wk.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: 2 animals given vitamin D alone.

DURATION OF EXPERIMENT: Up to 18 wk.

EXAM. TYPE: Behavior, histology

COMPOUND: Lead carbonate
000598630

REFERENCE: Hopkins, A.
Br. J. Indust. Med. 27:130-140, 1970.

OBSERVED NEUROTOXIC EFFECTS: Ten adults died, 2 were killed; 2 infants died, 1 was killed; 8 convulsed, 3 had limb weakness; no peripheral nervous system abnormality found, nor anemia nor punctate basophilia. Central nervous system findings to be given elsewhere; author discusses species differences.

ANIMALS: Baboons, 3 M, 9 F, 7.2-13.6 kg, F adult, M not full-grown; and 3 infant F, 2.8-3.3 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-135 mg/kg for 39-362 d, single and multiple doses.

ROUTE AND SITE: Intratracheal

CONTROL INFORMATION: Starting data and 12 healthy baboons used in other studies

DURATION OF EXPERIMENT: Up to 362 d.

EXAM. TYPE: Behavior, electrophysiology, histology

COMPOUND: Lead carbonate
000598630

REFERENCE: Hopkins, A.P. and Dayan, A.D.
Br. J. Indust. Med. 31:128-133, 1974.

OBSERVED NEUROTOXIC EFFECTS: Seizures, widespread cerebral edema, focal cortical necroses.

ANIMALS: 3 Baboons: 1 F, 11.7 kg; 1 F, 10.7 kg; 1 F, 2.8 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT:
1. 86 mg/kg, 5 doses in 122 d and 1 dose on d 137.
2. 94 mg/kg, 8 doses in 234 d.
3. 54 mg/kg, 1 dose and 2 larger doses in 84 d.

ROUTE AND SITE: Intratracheal

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Death on d 156, 265 and 117 respectively.

EXAM. TYPE: Behavior, histology

2002

COMPOUND: Lead carbonate

000598630

REFERENCE: Krigman, M.R., Druse, M.J., Traylor, T.D., Wilson, M.H., Newell, L.R., and Hogan, E.L.
J. Neuropath. Exp. Neurol. 33(1):58-73, 1974.

OBSERVED NEUROTOXIC EFFECTS: Neural tissue growth retarded. Myelin formation altered and its cerebral content reduced. Axons and number of myelin lamellae in the sheaths were reduced. Hypomyelination. Caudal paraplegia and medullary cysts. Abnormally small brains.

ANIMALS: Rats, Long-Evan newborns

PREPARATION AND DOSE or HISTORY OF PATIENT: 4% lead carbonate to nursing mothers and then to weanlings via diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 8 pups - no lead as controls.

DURATION OF EXPERIMENT: Sacr. after 30 d post-natal.

EXAM. TYPE: Biochemical, Histology, Ultra structural.

COMPOUND: Lead carbonate

000598630

REFERENCE: Krigman, M.R. and Hogan, E.L.
Env. Hlth. Persp. 7:187-199, 1974.

OBSERVED NEUROTOXIC EFFECTS: Brain growth retarded (mass, not cell numbers), with slow maturation, fewer synapses, hypomyelination, but essentially normal chemistry.

ANIMALS: Rats, Long-Evans, neonates with dams.

PREPARATION AND DOSE or HISTORY OF PATIENT: 4% in diet fed to dams and, at weaning, to litters.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Controls similarly treated, no lead.

DURATION OF EXPERIMENT: 30 d

EXAM. TYPE: Histology, biochemistry

COMPOUND: Lead carbonate

000598630

REFERENCE: Lampert, P.W. and Schochet, S.S.
J. Neuropath. Exp. Neurol. 27: 527-545, 1968.

OBSERVED NEUROTOXIC EFFECTS: Proliferation and degeneration of Schwann cells, with disintegration of myelin lamellae, new lamellae are formed and disintegrate, leaving remnants of basement membrane. Schwann cells proliferate along this membrane.

ANIMALS: 26 Long-Evans rats average 100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 4% in chow diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Chow only, "parallel groups"

DURATION OF EXPERIMENT: Serial sacr 2-12 mo.

EXAM. TYPE: Histology

VOL 3

COMPOUND: Lead carbonate

000598630

REFERENCE: Rosenblum, W.I. and Johnson, M.G.
Arch. Path. 85: 640-648, 1968.

OBSERVED NEUROTOXIC EFFECTS: Neonates exhibited an altered gait and loss of righting reflex. Neuropathologic findings induced excesses of fibrous intercapillary strands in cerebral sites, astrocytosis in the hippocampus, and altered properties of glia and/or cerebral tissues.

ANIMALS: Mice, Balb/c, pregnant F.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Diet contained 1% (in 3 cases 0.5%) lead carbonate after delivery.

ROUTE AND SITE: Oral

CONTROL INFORMATION: No lead carbonate

DURATION OF EXPERIMENT: Suckling neonates were killed at 14, 17, 20, 23d of age.

EXAM. TYPE: Clinical, histology

COMPOUND: Lead carbonate

000598630

REFERENCE: Sauerhoff, M.W. and Michaelson, I.A.
Science 182:1022-1024, 1973.

OBSERVED NEUROTOXIC EFFECTS: Hyperactivity, aggression, stereotype-behavior in neonates exposed via dam, starting at 4 wk of age; brain lead increased 8-fold, 20% less dopamine, no change in norepinephrine. Authors infer relationship of lead, dopamine, and behavior. (This report retracted in 1975 by Golter and Michaelson, see under Lead acetate).

ANIMALS: Rats, S-D, F, pregnant 16 d

PREPARATION AND DOSE or HISTORY OF PATIENT: 4% in diet for 16 d, then 40 ppm.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Pair-fed, matched controls

DURATION OF EXPERIMENT: Neonates serially sacr up to 29 d of age.

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Lead (II) nitrate (1:2)

010099748

REFERENCE: Markov, D.V. and Dimova, R.N.
Acta Neuropath. 28:25-35, 1974.

OBSERVED NEUROTOXIC EFFECTS: Ultrastructural changes seen only in microglial cells of parietal cortex: hypertrophy especially of endoplasmic reticulum, lipid inculsions.

ANIMALS: Rats, 11 littermates M and F, newborn.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.4% in drinking water from birth.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Mentioned-not described

DURATION OF EXPERIMENT: 9 mo.

EXAM. TYPE: Histology

COMPOUND: Leurocristine
000057227

REFERENCE: Anderson, P.J. Song, S.K. and Slotwiner, P.
J. Neuropath. Exp. Neurol. 26(1):15-24, 1967.

OBSERVED NEUROTOXIC EFFECTS: Peripheral and terminal motor endplates were degenerated when paralysis was maximal; interpretation uncertain according to authors. Other wise no peripheral nervous system abnormalities.

ANIMALS: 20 Rats, S-D, M, 150-250 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.3-0.4 mg/kg/d up to 4 d

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Matched controls untreated.

DURATION OF EXPERIMENT: 4 d

EXAM. TYPE: Histology

303

COMPOUND: Leurocristine
000057227

REFERENCE: Bradley, W.G.
J. Neurol. Sci. 10:133-162, 1970.

OBSERVED NEUROTOXIC EFFECTS: Acute: axonal degeneration in sciatic, posterior tibial, digital and intramuscular nerves; minor changes in dorsal root ganglia and anterior horn and in motor endplate axons. Chronic: Similar changes with denervation and terminal regeneration. Sciatic nerve conduction reduced to 81%.

ANIMALS: 27 Guinea-pigs, M, young (200-300 g), and old (>500 g), outbred.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 1 mg/kg one dose to 10 animals.
(2) 0.03 mg/kg, 2/wk to 17 animals.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 25 untreated controls.

DURATION OF EXPERIMENT: Up to 14 wk.

EXAM. TYPE: Electrophysiology, histology

304

COMPOUND: Leurocristine
000057227

REFERENCE: Bradley, W.G., Lassman, L.P., Pearce, G.W. and Walton, J.N.
J. Neurol. Sci. 10:107-131, 1970.

OBSERVED NEUROTOXIC EFFECTS: All treated over 2 mo. had mixed sensorimotor peripheral neuropathy, children less sensitive. Distal nerve conduction: increased latency to complete block. Main nerve trunks unaffected. Sural nerve biopsy: axonal degeneration. In 5 autopsies, distal muscles denervated. No signs of CNS damage, but ultrastructure not studied.

ANIMALS: Human: Cancer patients - 23 adults aged 26-63 year, 14 children aged 14 mo. to 13 yr. Follow-up data. Studied personally: 2 adults, 3 children.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.05 mg/kg/wk (one dose/wk) for up to 20 mo.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 20 mo.

EXAM. TYPE: Clinical, electrophysiology, histology (biopsy)

COMPOUND: Leurocristine
000057227

REFERENCE: Gottschalk, P.G., Dyck, P.J. and Kiely, J.M.
Neurol. 18: 875-882, 1968.

OBSERVED NEUROTOXIC EFFECTS: During third week of vincristine therapy, paresthesias in the fingers and toes appeared. Mild generalized muscle weakness and absence of muscle stretch reflexes noted at the end of seven weeks.

ANIMALS: 1 Human, F, age 63 yr

PREPARATION AND DOSE
or HISTORY OF PATIENT: 12 mg in 7 wk

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Group of rats, not described

DURATION OF EXPERIMENT: 7 wk

EXAM. TYPE: Neurological, physiological

COMPOUND: Leurocristine
000057227

REFERENCE: Joneja, M. and Ungthavorn, S.
Teratology 2:235-240, 1969.

OBSERVED NEUROTOXIC EFFECTS: Of 222 surviving fetuses, 36 had exencephaly, encephalocele, anopthalmia especially in C3H mice. 115/222 abnormal in some way.

ANIMALS: Mice: Inbred C3H/HeJ and DBA/2J and randombred Swiss ICR/Ha, F, pregnant.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.01% in saline on d 9 of gestation.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline only

DURATION OF EXPERIMENT: 8 d

EXAM. TYPE: Teratological

305>

COMPOUND: Leurocristine
000057227

REFERENCE: Levitt, L.P. and Prager, D.
Neurology 25:894-895, 1975.

OBSERVED NEUROTOXIC EFFECTS: "Mononeuropathy," acute, followed each of the last 2 single doses. Different nerve on each occasion. Claimed first report of an additional neurotoxic manifestation of vincristine.

ANIMALS: Human: one case, leukemic M aged 3 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg/28 d for 9 mo. with no ill effect; 18 mo. later one dose of 2 mg, repeated after 6 mo.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Over 3 mo. from last dose.

EXAM. TYPE: Behavior, electrophysiology

306

COMPOUND: Leurocristine
000057227

REFERENCE: McLeod, J.G. and Penny, R.
J. Neurol. Neurosurg. Psychiat. 32: 297-304, 1969.

OBSERVED NEUROTOXIC EFFECTS: The patients suffered paresthesias, areflexias (ankle) and slow motor and impaired sensory conduction in peripheral nerves which progressed or reversed after exposure stopped. Biopsy revealed demyelination and axonal degeneration in sural nerves; regeneration occurred after exposure stopped.

ANIMALS: Human: 9 patients, M & F, 18-79

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-15.5 mg (total) in 0.02-0.05 mg doses, no more than 5 doses/course

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical, electrophysiology, histology

COMPOUND: Leurocristine
000057227

REFERENCE: Moreas, G.R., D'Agostino, A.N. and Jarcho, L.W.
Arch. Neurol. 16:377-384, 1967.

OBSERVED NEUROTOXIC EFFECTS: Clinical neuropathy, mainly lower extremities, progressing to quadriparesis, time-related to compound. Necropsy: demyelination and axonal degeneration.

ANIMALS: Human: 3 cases of acute lymphoblastic leukemia

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.05 mg/kg, 0.1 mg/kg, 2 or more doses.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Lifetime of patients

EXAM. TYPE: Clinical, histology (necropsy)

COMPOUND: Leurocristine
000057227

REFERENCE: Shelanski, M.L. and Wisniewski, H.
Arch. Neurol 20:199-206, 1969.

OBSERVED NEUROTOXIC EFFECTS: Neurofibrillary proliferation found in all 3 cases. Authors feel effects were due to leurocristine and not the other chemotherapeutic agents administered.

ANIMALS: 3 Humans, acute leukemics, M 7 yr., F 13 yr and M 17 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT:
1. Dosage varied 1.0 mg-0.5 mg from Feg and Aug.
2. 1.7 mg, 3 doses, plus mercaptopurine 150 mg by mouth for 3 d and 75 mg after.
3. 2.7 mg, preceded by treatment with prednisone, mercaptopurine, and cyclophosphamide.

ROUTE AND SITE: 1. I.V., 2. ns., 3. I.V.

CONTROL INFORMATION: Control specimens mentioned, no details

DURATION OF EXPERIMENT: Weeks

EXAM. TYPE: Clinical exam, histopathology at autopsy.

3072

COMPOUND: Leurocristine
000057227

REFERENCE: Uy, Q.L., Moen, T.H., Johns, R.J. and Owens, A.H., Jr.
Johns Hopkins Med. J. 121:349-360, 1967.

OBSERVED NEUROTOXIC EFFECTS: Mice and rats: hindlimb paralysis; chromatolysis of dorsal root ganglia; later, degeneration of myelin and axis cylinders of sciatic nerves. No impairment of neuromuscular transmission or nerve conduction.

ANIMALS: Mice: BDF, (C57BL/6 x DBA/2), F, 20-25 g.
Rats: Lewis, F, 180-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT:
Mice: 1-8 mg/kg, one dose.
Rats: 0.25-1 mg/kg, one dose.

ROUTE AND SITE: Mice I.P., rats I.V.

CONTROL INFORMATION: Starved untreated animals.

DURATION OF EXPERIMENT: Serial sacr to 30 d

EXAM. TYPE: Behavior, histology, electrophysiology

308

COMPOUND: Leurocristine, sulfate (1:1) (salt)

2068782

REFERENCE: Clarke, J.I.R., Karpati,G., Carpenter, S. and Wolfe, L.S.
J. Neuropath. Exp. Neurol 31(2):247-266, 1972.

OBSERVED NEUROTOXIC EFFECTS: Lethargy, ataxia, paraplegia and quadriplegia after 24 hrs.

ANIMALS: Rats, Wistar, M, 100-150 gm.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.4 mg/kg for chemistry study.
(2) 0.3-0.4 mg/kg/d for 3 d as 0.1 mg/ml saline soln for histochemical studies.

ROUTE AND SITE: I.P.

CONTROL INFORMATION:

DURATION OF EXPERIMENT: (1) Sacr after 28 hr. (2) 4 d

EXAM. TYPE: Histochemistry, ultrastructural, chemistry

COMPOUND: Leurocristine, sulfate (1:1) (salt)

2068782

REFERENCE: Gottschalk, P.G., Dyck, P.J. and Kiely, J.M.
Neurol. 18: 875-882, 1968.

OBSERVED NEUROTOXIC EFFECTS: Peripheral neurophathy was produced. Axonal type degeneration of myelinated fibers. Most rats receiving more than 0.15 mg/kg/d died within four days. Those receiving 0.1 mg/kg/d died between eight and thirty days after initial injection.

ANIMALS: 70 Rats, S-D, M, 10-12 wk old, 174-300 gm

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 doses 2/wk which equal 0.05-0.5 mg/kg/d

ROUTE AND SITE: ns

CONTROL INFORMATION: Untreated controls

DURATION OF EXPERIMENT: 5-6d after admin to time of disorder manifestation

EXAM. TYPE: Behavior, histology

COMPOUND: Leurocristine, sulfate (1:1) (salt)
2068782

REFERENCE: Schlaepfer, W.W.
J. Neuropath. Exp. Neurol. 30(3): 488-505, 1971.

OBSERVED NEUROTOXIC EFFECTS: Axonal alterations of peripheral nerve. Axonal neurotubular disruption. Wallerian degeneration in the distal segment of nerve fibers.

ANIMALS: Rats, Albino, M, 300-350 gm.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1×10^{-3} M, 1×10^{-4} M or 1×10^{-5} M in saline solution.

ROUTE AND SITE: Endoneural inj.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 0.5-72 hr

EXAM. TYPE: Histochemistry, cytochemistry, ultrastructural

309>

COMPOUND: Leurocristine, sulfate (1:1) (salt)
2068782

REFERENCE: Schochet, S.S., Jr., Lampert, P.W. and Earle, K.M.
J. Neuropath. Exp. Neurol. 27:645-658, 1968.

OBSERVED NEUROTOXIC EFFECTS: 1. Human: seizures, neuronal changes (clumped Nissl substance, clear areas, acidophilic rhombohedral crystals)
2. Rabbits: similar effects: the clear areas were skeins of neurofilaments

ANIMALS: 1. Human: 1 case, F, Aged 2 1/2, acute leukemia, ending in autopsy.
2. 20 Rabbits, NZ White, 2.5 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1. Human: 15 mo. history of cytotoxic drugs including vincristine i.v.; then 3 mg given intrathecally, and 200 ml of cerebrospinal fluid exchanged for 200 ml saline.
2. Rabbits: 0.001-0.2 mg/kg one dose intracisternally.

ROUTE AND SITE: See above

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Rabbits: 1-4 d

EXAM. TYPE: Autopsy, histology

310

COMPOUND: Leurocristine sulfate

REFERENCE: Seil, F.J. and Lampert, P.W.
Exp. Neurol. 21: 219-230, 1968

OBSERVED NEUROTOXIC EFFECTS: Neurofibrillary tangles and neuronal degeneration; starting with clumping of argentophilic neurofilaments around the nucleus. Persistent after withdrawal of compound.

ANIMALS: In vitro cultures of fetal rabbit spinal cord and dorsal root ganglia

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5-20 ng/drop of medium, changed twice a week, starting serially at 17-26 d in vitro. Exposures lasted in all 31 hr to 14 d.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Histology

COMPOUND: Leurocristine, sulfate (1:1) (salt)
2068782

REFERENCE: Seil, F.J., Lampert, P.W. and Klatzo, I.
J. Neuropath. Exp. Neurol. 28: 74-85, 1969.

OBSERVED NEUROTOXIC EFFECTS: Induced neurofibrillary spheroids filled the cytoplasm of the cells exposed to aluminum phosphate, and the nuclei were displaced. The spheroids were compared with those induced by vincristine sulfate. The author claimed the former were like those of postencephalitic parkinsonism and the latter like those of Alzheimer's disease.

ANIMALS: In vitro cultures of spinal cord and dorsal root ganglia from fetal NZ White rabbits.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5-20 ng/drop of medium for 31hr to 14 d, medium renewed twice weekly

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Untreated cultures

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Light and electron microscopy

COMPOUND: Lithium carbonate

000554132

REFERENCE: Vacaflor, L., Lehmann, H.E. and Ban, T.A.
J. Clin. Pharm. 10: 387-389, 1970.

OBSERVED NEUROTOXIC EFFECTS: The patients experienced toxic confusion within 2 wk of treatment (impaired consciousness, clonic limb movements), which reversed in 1 wk after treatment was stopped and did not reappear after treatment was reinstituted. One case (gravida 7 mo, history of mania) given 900-1200 mg/d developed hand tremor, whereupon treatment was stopped; after delivery she took unknown amount of unprescribed compound (serum 5mEq/liter) and had 5 d of coma, spasticity of limbs, and convulsions.

ANIMALS: Human: 5 cases of side-effects attributed to compound, all over 50 yr old

PREPARATION AND DOSE or HISTORY OF PATIENT: 600 mg/d increasing to 900-1200 mg/d, producing only serum 0.97-1.53 mEq/liter

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

311A

COMPOUND: Lithium chloride

007447418

REFERENCE: Benowitz, L.J. and Sperry, R.W.
Exp. Neurol. 40:540-546, 1973.

OBSERVED NEUROTOXIC EFFECTS: No effect on memory 20 min after treatment, but amnesia 24 hr afterwards, if treated 4 min before training (less so if treated 2 min before, and no effect if treated 10 min after training). Delayed effect on development of long term memory in chicks.

ANIMALS: Cockerels, White Leghorn, 1 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.245 mg/chick, before or after memory-training

ROUTE AND SITE: Injected into 2 cerebral hemispheres, 1/2-dose to each

CONTROL INFORMATION: Vehicle only (some), sham training (others)

DURATION OF EXPERIMENT: 10 sec to 2 hr.

EXAM. TYPE: Behavior

312

COMPOUND: D-Lyseramide, N-N-diethyl ester, tartrate (LSD)

REFERENCE: Diab, I.M., Freedman, D.X. and Roth, L.J.
Science 173:1022-1024, 1971.

OBSERVED NEUROTOXIC EFFECTS: Free LSD generally distributed in pituitary, pineal, cerebellum, hippocampus, choroid plexus. Bound LSD localized in cortical neurons, caudate nucleus, midbrain, medulla, epithelium of choroid plexus.

ANIMALS: Rats, S-D, M, 100-125 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mcg/g, or 1.7 mcg/g of labeled compound.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 5-60 min.

EXAM. TYPE: Autoradiography

COMPOUND: Malic acid, L(+)-

REFERENCE: Curtis. D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Malonic acid

000141822

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, δ-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

313A

COMPOUND: Malonic acid, amino-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, δ-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

314

COMPOUND: Malonic acid, aminoethyl-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Mandelic acid, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 6.0 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Manganese
007439965

REFERENCE: Cotzias, G.C., Horiuchi, K., Fuenzalida, S. and Mena, I.
Neurology 18:376-382, 1968.

OBSERVED NEUROTOXIC EFFECTS: "Healthy" miners had more tissue manganese and cleared Manganese faster than controls or chronic-poisoned grps from tissues, although clearance from bloodstream was slower. Neuropathy continued in poisoned grp. Authors conclude that hig tissue Manganese not needed for neuropathy to continue; thus chelation therapy logically useless.

ANIMALS: Humans: 20 healthy miners M, aged 23-60 yr.
18 patients with chronic Manganese poisoning M, aged 18-56 yr.
19 hospital staff, M and F, aged 20-30 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1-20 yr industrial exposure continuing.
(2) Exposure terminated 2-27 yr before study.
(3) No exposure.
All given ^{54} Manganese for clearance studies.

ROUTE AND SITE: I.V., antecubital

CONTROL INFORMATION: Grps (1) and (3) treated as controls.

DURATION OF EXPERIMENT: About 1 mo.

EXAM. TYPE: Biochemical

315

COMPOUND: Manganese
007439965

REFERENCE: Mena, I., Marin, O., Fuenzalida, S. and Cotzias, G.C.
Neurology 17: 128-136, 1967.

OBSERVED NEUROTOXIC EFFECTS: Transient psychiatric symptoms (long list) followed by permanent neurologic (partly extrapyramidal) changes, only in the poisoned group. "Healthy" miners eliminated labeled Mn faster than either poisoned or non-exposed control groups.

ANIMALS: Human: 114 Mn miners, clinically "healthy", of whom 14 were selected for isotope studies: M ages 20-60 (av. 37 yr).
13 in-patients with chronic Mn poisoning; ages 18-56 yr (av. 50)

PREPARATION AND DOSE or HISTORY OF PATIENT: Industrial exposure; clinical histories and lab studies performed.

ROUTE AND SITE: Mainly inhalation of dusts

CONTROL INFORMATION: Medical workers, 4 M, 4 F, aged 20-30.

DURATION OF EXPERIMENT: 20-30 d for each case

EXAM. TYPE: Behavior, laboratory, isotope studies.

316

COMPOUND: Manganese
007439965

REFERENCE: Nichols, R.A. and Nakajima, Y.
Brain Res. 86: 493-498, 1975.

OBSERVED NEUROTOXIC EFFECTS: Manganese inhibited the generation of the IPSP (sic) of the stretch receptor neuron but did not affect the action potential of the soma and had no effect on GABA-induced increase of conductance. Manganese was interpreted to affect coupling of excitation with GABA secretion at the presynaptic site of the inhibitory synapse.

ANIMALS: In vitro: slow adapting stretch receptors from 8th thoracic segment of lobster (H. americanus) and crayfish (Oronectes), or from the 2nd-3rd abdominal segment of crayfish.

PREPARATION AND DOSE or HISTORY OF PATIENT: Mn at 0-5 mM

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Zero treatment

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Manganese
007439965

REFERENCE: Prakash, N.J., Fontana, J. and Hankin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: Inhibited ($Na^+ + K^+$) ATPase, although never more than 20%, even at 0.2 mM. Inhibition involved blockage of norepinephrine.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Mn^{++} chloride added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

COMPOUND: Manganese
007439965

REFERENCE: Prasad, K.N.
Exp. Neurol. 45:554-557, 1974.

OBSERVED NEUROTOXIC EFFECTS: Adenyl cyclase inhibited, cAMP phosphodiesterase stimulated by manganese. Differentiated cells more sensitive to manganese than undifferentiated.

ANIMALS: In vitro cultured mouse neuroblastoma cells

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 or 10 mM in medium

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Mentioned, no details.

DURATION OF EXPERIMENT: 3 or more d

EXAM. TYPE: Biochemistry

3127

COMPOUND: Manganese
007439965

REFERENCE: Rosenstock, H.A., Simons, D.G. and Meyer, J.S.
J. Am. Med. Assn. 217:1354-1358, 1971.

OBSERVED NEUROTOXIC EFFECTS: Impairment of gait and station, dysarthric speech and deterioration of fine motor coordination. Headaches, anxiety and irritability.

ANIMALS: Human: one, M, 22 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to fumes present in a steel foundry over a two year period. After that too disabled to work, 14 yr later was confined to wheelchair.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 14 mo. of exposure

EXAM. TYPE: Clinical

318

COMPOUND: Manganese
007439965

REFERENCE: Smyth, L.T., Ruhf, R.C., Whitman, N.E. and Dugan, T.
J. Occup. Med. 15:101-109, 1973.

OBSERVED NEUROTOXIC EFFECTS: 5 Subjects with signs of Parkinsonism were examined, removed from exposure, and reexamined after 3 mo. Reversible manifestations (loss of associated arm movements) had disappeared, irreversible ones had not progressed. Authors concluded that Manganese exposure was the cause, although urine values were not high (but bile is the main route of excretion of Manganese). Blood chemistry was inconclusive.

ANIMALS: Human: 142 employees of a steelworks producing ferromanganese alloy, 71 directly exposed, 71 not directly exposed.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to fume and dust, 0.12-13.3 mg/m^3 (TLV = 5 mg/m^3) up to 26 yr. Fume was mainly Mn_3O_4 <2 mc in size. Dust was mainly FeMn, also MnO, Mn_3O_4 and Fe_2O_3, 95% <5 mc in size, and respirable.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: The 71 not exposed were carefully matched.

DURATION OF EXPERIMENT: Over 3 mo.

EXAM. TYPE: Clinical

COMPOUND: Manganese
007439965

REFERENCE: Tanaka, S. and Lieben,
J. Arch. Env. Hlth. 19:674-684, 1969.

OBSERVED NEUROTOXIC EFFECTS: Weakness, tremors, disturbed gait, motor impairment of extremities. Recovery, none to partial.

ANIMALS: Human, 3 selected cases of industrial exposure

PREPARATION AND DOSE or HISTORY OF PATIENT: Up to >100 mg/m^3 in air (dust) for 1-17 yr.

ROUTE AND SITE: Inhalation and skin contact

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Years

EXAM. TYPE: Clinical, clinicochemical

COMPOUND: Manganese (II) chloride (1:2)
0096250

REFERENCE: Chandra, S.V. and Sur, R.N.
Env. Res. 3:417-424, 1970.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, EEG changes, scattered degeneration of neurons in cerebral and cerebellar cortex.

ANIMALS: 40 Rabbits, M, av. 1.5 kg. 30 had surgical impl of brain cannulae.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5 mg in 0.1 ml saline/2 d for 15 d

ROUTE AND SITE: Intraventricular

CONTROL INFORMATION: 10 normal controls, 10 had cannula impl and 0.1 ml saline inj.

DURATION OF EXPERIMENT: Serial sacr 0 hr to 15 d

EXAM. TYPE: Behavior, autopsy, histology

319

COMPOUND: Manganese (II) chloride (1:2)
0096250

REFERENCE: Meiri, U. and Rahamimoff, R.
Science 176:308-309, 1972.

OBSERVED NEUROTOXIC EFFECTS: Managanese ions blocked synaptic transmission at the neuromuscular junction. The inhibition produced is reversible.

ANIMALS: In vitro preparation of frog sartorius muscle.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mM $MnCl_2$; 0.07-1 mM Mn^{2+}

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Electrophysiology

320

COMPOUND: Manganese, cyclopentadienyltricarbonyl
012079651

REFERENCE: Arkhipova, O.G.
Fed. Proc. 23: T51-T54, 1964.

OBSERVED NEUROTOXIC EFFECTS: Damage to nervous system indicated by trembling, paresis of limbs and reduced neuromuscular excitability.

ANIMALS: Rats, white; Mice, white; Rabbits; Guinea-pigs

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: LD_{50} was 80 mg/kg, MLD 40 mg/kg
Mice: LD_{50} was 150 mg/kg, MLD 80-100 mg/kg
Rats, rabbits, guinea-pigs: Exposed to 0.0007-0.001 mg/liter of air for 10 mo

ROUTE AND SITE: Inhalation. Route of LD and MLD doses as (but not inhalation).

CONTROL INFORMATION: Yes, but not described

DURATION OF EXPERIMENT: 10 mo

EXAM. TYPE: Clinical

COMPOUND: 3-Mercaptopropionic acid

REFERENCE: Arnaiz, G.R. deL., de Canal, M.A. and DeRobertis, E.
J. Neurochem. 19:1379-1385, 1972.

OBSERVED NEUROTOXIC EFFECTS: Dose-related convulsant properties studied in cerebellum. Glutamate decarboxylase and GABA fell, GABA-aminotransferase rose, and dose-related changes were seen in Purkinje cells. From these and other enzyme and amino-acid changes the authors inferred that the compound causes imbalance among the excitatory-inhibitory amino acids.

ANIMALS: Rats, Wistar, 100-150 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 35-150 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls no treatment.

DURATION OF EXPERIMENT: 60 min

EXAM. TYPE: Biochemistry, histology, behavior

COMPOUND: Manganese dioxide
001313139

REFERENCE: Abd el Naby, S. and Hassanein, M.
J. Neurol. Neurosurg. Psychiat. 28: 282-288, 1965.

OBSERVED NEUROTOXIC EFFECTS: The subjects experienced insidious onset with fatigue and inertia; then weak, stiff gait, parkinsonian-type imbalance, motor signs cerebellar, pyramidal, and/or extrapyramidal; sleep disturbances, psychoses and emotional lability. Permanent disabilities included the use of legs, and neurological signs continued to progress after exposure stopped; only psychic changes regressed.

ANIMALS: Human: 45 miners, M, 21-54

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to dust for 5 mo to 25 yr

ROUTE AND SITE: Dermal, inhalation, possibly ingestion too.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: na

EXAM. TYPE: Clinical

3x1x

COMPOUND: 3-Mercaptopropionic acid

REFERENCE: Horton, R.W. and Meldrum, B.S.
Br. J. Pharmac. 49: 52-63, 1973.

OBSERVED NEUROTOXIC EFFECTS: Seizures, photic stimulation, EEG changes, inhibition of brain glutamate carboxylase were caused by 3-mercaptopropionic acid more strongly than by allylglycine or 4-deoxypyridoxine HCl. Thus the authors concluded that seizures were due to depletion of glycine and γ-aminobutyric acid (GABA).

ANIMALS: Mice, CFW or BALB/C, M, 20-30 g
10 Baboons (Papio papio), adolescent, from Senegal, 3-6 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: ED_{50} and latency 0.27 mmol/kg, 4.5 min.
Baboons: ED_{50} and latency 0.28 mmol/kg, 4 min.

ROUTE AND SITE: Mice I.P., Baboons I.V.

CONTROL INFORMATION: Timed studies

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Mice: behavior, biochemistry; baboons: polygraph.

322

COMPOUND: 3-Mercaptopropionic acid

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Mercuric bichloride

007487947

REFERENCE: Chang, L.W., Desnoyers, P.A., and Hartmann, H.A.
J. Neuropath. Exp. Neurol. 31(3):489-501, 1972.

OBSERVED NEUROTOXIC EFFECTS: Poisoning produced initial decrease in RNA content followed by partial increase of RNA after prolonged intoxication. Cell volume decreased. Moderate increase in RNA was noted in anterior horn motoneurons.

ANIMALS: 18 Rats

PREPARATION AND DOSE or HISTORY OF PATIENT: Daily dosage of 1.2 mg/kg body weight.

ROUTE AND SITE: Oral, stomach tube, S.C.

CONTROL INFORMATION: 6 Rats

DURATION OF EXPERIMENT: Serial sacr 1 wk, 2 wks, 6 wks

EXAM. TYPE: Histology, quantitative, cytochemical

COMPOUND: Mercuric bichloride

007487947

REFERENCE: Chang, L.W. and Hartmann, H.A.
Exp. Neurol. 35:122-137, 1972.

OBSERVED NEUROTOXIC EFFECTS: General distribution of mercury parallel to gross neuropathology; intracellular binding to membraneous structures in cytoplasm, minimally in nucleus.

ANIMALS: Rats, S-D, adult M

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg/d

ROUTE AND SITE: Gavage or S.C.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: 1 d to 11 wk, serial

EXAM. TYPE: Histochemistry

323>

COMPOUND: Mercuric bichloride

007487947

REFERENCE: Takeda, Y., Kunugi, T., Hoshino, O. and Ukita, T.
Tox. Appl. Pharm. 13: 156-164, 1968.

OBSERVED NEUROTOXIC EFFECTS: Alkyl mercury compounds excreted more slowly than inorganic or aryl compounds. Metabolism varied with C-chain length. Distribution in brain and reported neurotoxicity were related to structure of compound.

ANIMALS: Rats, Donryu, aged 7 wk

PREPARATION AND DOSE or HISTORY OF PATIENT: Compounds labeled with ^{203}Hg; mercuric chloride 3 mg/kg, others 10 mg/kg (one dose).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial 1-8 d

EXAM. TYPE: Biochemistry

324

COMPOUND: Mercuric (II) nitrate
010045940

REFERENCE: Fox, J.H., Patel-Mandlik, K. and Cohen, M.M.
J. Neurochem 24:757-762, 1975.

OBSERVED NEUROTOXIC EFFECTS: No effect on respiration or metabolism.

ANIMALS: Guinea-pig brain slices, in vitro.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1-1.0 mM in medium.

ROUTE AND SITE: In vitro incubation

CONTROL INFORMATION: Mercury-free medium used for control.

DURATION OF EXPERIMENT: 1 hr in some cases

EXAM. TYPE: Biochemistry

COMPOUND Mercury
007439976

REFERENCE: Chang, L.W., Optiz, J.M., Pallister, P.D., Gilbert, E.F. and Viseskul, C.
Acta Neuropath. (Berl.) 26:275-284, 1973.

OBSERVED NEUROTOXIC EFFECTS: Disintegration of granular layer, disapperance of Purkinje cells with Bergmann's fiber proliferation and demyelination of fiber tracts observed in cerebellum. Extensive proliferation of astrocyte fibers and characteristic focal demyelination and loosening of myelin sheaths in many nerve fibers.

ANIMALS: 1 case study of 21 yr female.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Accidental exposure to mercury-containing herbicide during childhood.

ROUTE AND SITE: Ingestion

CONTROL INFORMATION: Experimental rat poisoned with mercury.

DURATION OF EXPERIMENT: 19 yrs.

EXAM. TYPE: Light and election microscopy.

COMPOUND Mercury

007439976

REFERENCE: Danziger, S.J. and Possick, P.A.
J. Occup. Med. 15:11-20, 1973.

OBSERVED NEUROTOXIC EFFECTS: Symptoms: 6 insomnia, 5 hard-of-hearing, 4 oral phenomena, 3 peripheral neuropathy, 2 depression, 1 severe oral and sensory disturbance with tremors and irritability. Signs: 59 myopia, 12 dermographism, 9 hearing loss, 2 hyperesthesia, 1 dental oral and ocular disorders. High urine Hg and 6 cases of proteinuria.

ANIMALS: Human: 75 workers (gender ns) calibrating lab glassware in 13 factories in New Jersey, ages 20-60+

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure from 0.5 to 40+ y, skin contact; vapor 0-0.3 mg/m^3 in breathing zone, to 1.03 elsewhere. (TLV is 0.1, 0.05 proposed).

ROUTE AND SITE: Skin, inhalation, perhaps ingestion

CONTROL INFORMATION: 4 foremen claiming to work in uncontaminated areas, and the research team.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical, behavior, blood and urinalysis, environmental

325

COMPOUND: Mercury

00743996

REFERENCE: Prakash, N.J., Fontana, J. and Henkin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: At concentrations over 0.01 mM, Hg^{++} completely inhibited (Na^{+} + K^{+}) ATPase. Inhibition involved blockage of norepinephrine and choline uptake.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Hg^{++} chloride added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

326

COMPOUND: Mercury

007439976

REFERENCE: Smith, R.G., Vorwald, A.J., Patil, L.S. and Mooney, T.F. Am. Indust. Hyg. Assn. J. 31:687-700, 1970.

OBSERVED NEUROTOXIC EFFECTS: Anorexia, insomina, tremors, other signs.

ANIMALS: Human: 642 workers from 21 chloralkali plants in U.S. and Canada.

PREPARATION AND DOSE or HISTORY OF PATIENT: Time-weighted av exposures approx. 0 to 0.27 mg/m^3, 85% $\leq$ 0.1 mg/m^3.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: 382 non-exposed workers

DURATION OF EXPERIMENT: 1 yr.

EXAM. TYPE: Full medical.

COMPOUND Mercury

007439976

REFERENCE: Vroom, F.Q. and Greer, M. Brain 95· 305-318, 1972.

OBSERVED NEUROTOXIC EFFECTS: Irritability and poor concentration (transient), memory defects (permanent), suggesting temporal lobe lesions; neuropsychology suggesting general cortical dysfunction; abnormal EEG; parkinsonianism; severe tremors in all; peripheral nervous system involvement; electromyography indicating denervation.

ANIMALS: Human: 9 selected employees of a thermometer factory where industrial negligence had produced an epidemic of signs.

PREPARATION AND DOSE or HISTORY OF PATIENT: About 3 yr exposure, less in some cases.

ROUTE AND SITE: Inhalation, skin contact, ingestion

CONTROL INFORMATION: Up to 40 normal subjects for various tests

DURATION OF EXPERIMENT: Up to 20 mo after diagnosis

EXAM. TYPE: Electrophysiology, neuropsychology, behavior, chemistry

COMPOUND: Mercury, (acetato)methyl-

REFERENCE: Carmichael, N., Cavanagh, J.B. and Rodda, R.A.
Acta. Neuropath. 32(2):115-125, 1975.

OBSERVED NEUROTOXIC EFFECTS: Severe ataxia. Degenerative changes seen in primary sensory ganglion cells, in both Purkinje and granule cells of the cerebellum, and in cells of the forebrain. Wallerian degeneration of sensory neurones, widespread pyknosis of cerebellum, symmetrical changes in cerebral cortex.

ANIMALS: Rabbits, New Zealand, White, M and F, young 1.0-2.5 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.5 mg/kg/d for 3-4 d, total 22.5 or 30 mg/kg.

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: 2 rabbits.

DURATION OF EXPERIMENT: Serial sacr: 1, 2, 8 d

EXAM. TYPE: Histology, vascular

>327<

COMPOUND: Mercury, (acetato)methyl-

REFERENCE: Kim, S.U.
Exp. Neurol. 32:237-246, 1971.

OBSERVED NEUROTOXIC EFFECTS: Vacuolar degeneration especially in granule and Purkinje cells. Axonx and melin sheaths degenerated, cytoplasmic organelles affected but not nuclear structures.

ANIMALS: Slices of newborn mouse cerebellum in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 mM in medium

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: 5 h to 2½ d

EXAM. TYPE: Histology

328

COMPOUND: Mercury, butyl-chloro-

000543635

REFERENCE: Takeda, Y., Kunugi, T., Hoshino, O. and Ukita, T.
Tox. Appl. Pharm. 13: 156-164, 1968.

OBSERVED NEUROTOXIC EFFECTS: Alkyl mercury compounds excreted more slowly than inorganic or aryl compounds. Metabolism varied with C-chain length. Distribution in brain and reported neurotoxicity were related to structure of compound.

ANIMALS: Rats, Donryu, aged 7 wk

PREPARATION AND DOSE
or HISTORY OF PATIENT: Compounds labeled with ^{203}Hg; mercuric chloride 3 mg/kg, others 10 mg/kg (one dose).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial 1-8 d

EXAM. TYPE: Biochemistry

COMPOUND: Mercury (I) chloride

007546307

REFERENCE: Davis, L.E., Wands, J.R., Weise, S.A., Price, D.L. and Girling, E.F.
Arch. Neurol. 30:428-431, 1974

OBSERVED NEUROTOXIC EFFECTS: Dementia, recent memory loss, sensorineural loss, ataxia, coarse tremors. Autopsy revealed small brains, loss of cerebellar granular cells, Hg in neuronal cytoplasm (especially choroid plexus).

ANIMALS: 2 Human patients: (1) F, 63 yr and (2) F, 56 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 120 mg as laxative tablet, twice daily for: (1) 25 yr, (2) 6 yr prior to death.

ROUTE AND SITE: Oral

CONTROL INFORMATION: No controls

DURATION OF EXPERIMENT: (1) 25 yr, (2) 6 yr

EXAM. TYPE: Behavior, Hospital investigations.

COMPOUND: Mercury (II) chloride

007487947

REFERENCE: Chang, L.W. and Hartmann, H.A.
Acta Neuropath. 20:316-334, 1972.

OBSERVED NEUROTOXIC EFFECTS: Pathological manifestations in dorsal and ventral root fibers and sciatic nerve. Axonal degeneration. Disoriented myelin layers.

ANIMALS: Rats, Adult, M

PREPARATION AND DOSE or HISTORY OF PATIENT: 1.0 mg/kg/d.

ROUTE AND SITE: Oral and injections

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Serial sacr. 5 hr, 12 hr, 1 d, 4 d, 1 wk, 6 wk, 11 wk.

EXAM. TYPE: Ultrastructural, histology

329

COMPOUND: Mercury, chloroethyl-

000107277

REFERENCE: Hay, W.J., Rickards, A.G., McMenemey, W.H. and Cumings, J.N.
J. Neuro. Neurosurg. Psychiat. 26: 199-202, 1963.

OBSERVED NEUROTOXIC EFFECTS: The brain cortex was selectively damaged, especially the calcarine, parastriate, motor and sensory areas and the caudal part of first temporal gyrus. A loss of neurons, a porous underlying white matter, swollen oligodendrocytes were observed. There was a high concentration of mercury in the corpus callosum. The patient experienced blurred vision, deafness, ataxic dysarthria, incoordination and weakness of arms and legs.

ANIMALS: Human: M, 29 (one case)

PREPARATION AND DOSE or HISTORY OF PATIENT: Occupational exposure of 7 wk before onset of symptoms, died 25 wk after first exposure

ROUTE AND SITE: ns

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 25 wk

EXAM. TYPE: Clinical, histology

330

COMPOUND: Mercury, chloroethyl-

000107277

REFERENCE: Kasuya, M.
Tox. Appl. Pharm. 32:347-354, 1975.

OBSERVED NEUROTOXIC EFFECTS: Compound inhibited outgrowth. Vitamin E protected against toxicity, less potently against ethylmercuric chloride than methylmercuric chloride. Interpreted that alkyl mercurials interact with membranes to produce nerve degeneration.

ANIMALS: In vitro slices of newborn rat cerebella

PREPARATION AND DOSE or HISTORY OF PATIENT: 6×10^{-6} to 2×10^{-5} M; in presence of ethanol 0.1-0.4%, glucose 550 mg/100 ml, and vitamin E (DL-α-tocopherol acetate) 0-2×10^{-5} M.

ROUTE AND SITE: Culture medium

CONTROL INFORMATION: Zero levels of various additives to medium

DURATION OF EXPERIMENT: 4 d

EXAM. TYPE: Microscopic outgrowth of neurons and fibroblasts

COMPOUND: Mercury, chloroethyl-

000107277

REFERENCE: Takeda, Y., Kunugi, T., Hoshino, O. and Ukita, T.
Tox. Appl. Pharm. 13: 156-164, 1968.

OBSERVED NEUROTOXIC EFFECTS: Alkyl mercury compounds excreted more slowly than inorganic or aryl compounds. Metabolism varied with C-chain length. Distribution in brain and reported neurotoxicity were related to structure of compound.

ANIMALS: Rats, Donryu, aged 7 wk

PREPARATION AND DOSE or HISTORY OF PATIENT: Compounds labeled with ^{203}Hg; mercuric chloride 3 mg/kg, others 10 mg/kg (one dose).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial 1-8 d

EXAM. TYPE: Biochemistry

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Carmichael, N., Cavanagh, J.B., and Rodda, R.A.
Acta Neuropath. 32(2):115-125, 1975.

OBSERVED NEUROTOXIC EFFECTS: Severe ataxia. Primary sensory ganglion cells, cerebellar Purkinje and granule cell and forebrain cell degeneration. Wallerian degeneration of sensory neurones, widespread pyknosis of cerebellum, symmetrical changes in cerebral cortex.

ANIMALS: Rabbits, New Zealand, White, M and F, young 1.0-2.5 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.5 mg/kg/d for 3-4 d, as suspension (5 mg/ml) in 50% polyethylene glycol 400. Total 22.5 or 30 mg/kg.

ROUTE AND SITE: S.C., neck

CONTROL INFORMATION: 2 rabbits

DURATION OF EXPERIMENT: Serial sacr: 1,2,8d.

EXAM. TYPE: Histology, vascular.

331

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Chang, L.W. Desnoyers, P.A., and Hartmann, H.A.
J. Neuropath. Exp. Neurol. 31(3):489-501, 1972.

OBSERVED NEUROTOXIC EFFECTS: Continuous decrease in RNA content in spinal ganglion neurons. Except for cell swelling during first week of methylmercury poisoning, cell volume decreased after poisoning. Moderate increase in RNA after poisoning was noted in anterior horn motoneurons.

ANIMALS: 9 Rats, S-D (Holtzman), 150 g

PREPARATION AND DOSE or HISTORY OF PATIENT: Daily dosage of 1.0 mg/kg body weight

ROUTE AND SITE: Orally, stomach tube, S.C.

CONTROL INFORMATION: 6 Rats

DURATION OF EXPERIMENT: Serial sacr 1 wk, 2 wks, 6 wks, 11 wks.

EXAM. TYPE: Histology, quantitative, cytochemical studies.

3327

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Chang, L.W. and Hartmann, H.A.
Exp. Neurol. 35:122-137, 1972.

OBSERVED NEUROTOXIC EFFECTS: General distribution of mercury parallel to gross neuropathology; intracellular binding to membraneous structures in cytoplasm, minimally in nucleus.

ANIMALS: Rats, S-D, adult M

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg/d

ROUTE AND SITE: Gavage or S.C.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: 1 d to 11 wk, serial

EXAM. TYPE: Histochemistry

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Chang, L.W. and Hartmann, H.A.
Acta Neuropath. 20:316-334, 1972.

OBSERVED NEUROTOXIC EFFECTS: After 4 days, mercury apparent in axoplasm. Dorsal root fiber pathology after 1 wk. Axonal degeneration with destruction of myelin. Limited damage to ventral root fibers and extensive damage to sciatic nerve in 2nd wk. Phagocytosis by Schwann cells observed.

ANIMALS: Rats, adult M

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg/d

ROUTE AND SITE: Oral or I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Serial to 11 wk.

EXAM. TYPE: Histology

COMPOUND: Mercury, chloromethyl-

REFERENCE: Fehling, C., Abdulla, M., Brun, A., Dictor, M., Schutz, A. and Skerfving, S. Toxicol. Appl. Pharm. 33:27-37, 1975.

OBSERVED NEUROTOXIC EFFECTS: Waddling gait, cross of hindlimbs and severe involvement of righting reflexes. Wallerian degeneration and edema and degeneration of sensory ganglia. Partial reversible peripheral neuropathy.

ANIMALS: 30 Rats, Wistar, M, 135-170 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 or 40 mg Hg/kg/d as soln with dilute sodium hydroxide and 20% (w/w) egg albumin.

ROUTE AND SITE: I. Tub.

CONTROL INFORMATION: 10 controls mercury-free albumin soln.

DURATION OF EXPERIMENT: 15 d

EXAM. TYPE: Neurological, chemical, nerve conduction velocity, histopathology.

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Garman, R.H., Weiss, B. and Evans, H.L. Acta Neuropath. 32:61-74, 1975.

OBSERVED NEUROTOXIC EFFECTS: Neuronal damage in cerebral cortex, eosinophilic neuron degeneration, loss of Nissl substance, impairment of touch and vision. Loss of proprioceptive sense, incoordination, astereognosis.

ANIMALS: 14 Squirrel Monkeys, Saimiri sciureus, Male
6 Monkeys, Macaca, Male

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.4-4 mg Hg/kg/wk.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Sacr. at various intervals.

EXAM. TYPE: Clinicopathology, autoradiography, necropsy, histology

334

COMPOUND: Mercury, chloromethyl-
000115093

REFERENCE: Harris, S.B., Wilson, J.G. and Printz, R.H.
Teratology 6:139-142, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hydrocephalus among surviving fetuses. Compound produced significant amounts of embryotoxicity, and also produced some maternal toxicity.

ANIMALS: Golden hamsters, F, pregnant, at least 134

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 2-8 mg/kg in carboxymethylcellulose (0.2%) one time, d 5-10 of pregnancy;
(2) Groups of 20 given 8 mg/kg on d 5, 8 or 9.
(3) 10 animals given 4 mg/kg on d 8.
(4) Chronic: 1, 4, or 2 mg/kg/d for 14 d.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Control group vehicle only.

DURATION OF EXPERIMENT: Sacr on d 15 of pregnancy

EXAM. TYPE: Teratological

COMPOUND: Mercury, chloromethyl-
000115093

REFERENCE: Iverson, F., Downie, H., Paul, C. and Trenholm, H.L.
Tox. Appl. Pharm. 24:545-554, 1973.

OBSERVED NEUROTOXIC EFFECTS: Loss of muscular control (neurotoxicity) 1-2 wk after treatment, some cases. In Central nervous system levels ranked cerebrum, cerebellum, cord, dose-related; decay (elimination) rate not dose-related but biphasic.

ANIMALS: Guinea-pigs, English, F, 400-500 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: Acute toxicity
I.P.: 1.5-9.1 mg Hg/kg
P.O.: 4-30 mg Hg/kg
in 5mM sodium carbonated at 0.5 ml/100 g to 10 animals each dose.

ROUTE AND SITE: Oral, i.p.

CONTROL INFORMATION: Controls: sodium carbonate treatment.

DURATION OF EXPERIMENT: Serial sacr, 1-49 d after dose.

EXAM. TYPE: Mortality, biochemistry

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Kasuya, M.
Tox. Appl. Pharm. 32:347-354, 1975.

OBSERVED NEUROTOXIC EFFECTS: Compound inhibited outgrowth. Vitamin E protected against toxicity, less potently against ethylmercuric chloride than methylmercuric chloride. Interpreted that alkyl mercurials interact with membranes to produce nerve degeneration.

ANIMALS: In vitro slices of newborn rat cerebella

PREPARATION AND DOSE or HISTORY OF PATIENT: 10^{-5} M; in presence of ethanol 0.1-0.4%, glucose 550 mg/100 ml, and vitamin E (DL-α-tocopherol acetate) 0-2 x 10^{-5} M.

ROUTE AND SITE: Culture medium

CONTROL INFORMATION: Zero levels of various additives to medium

DURATION OF EXPERIMENT: 4 d

EXAM. TYPE: Microscopic outgrowth of neurons and fibroblasts

335A

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Khera, K.S.
Teratology 8:293-304, 1973.

OBSERVED NEUROTOXIC EFFECTS: Mercury 6.6 ppm in maternal brain. Fetal cerebellum: transient external granular layer thinner than in controls; cell aggregates in incipient molecular layer more common than in controls, changes dose-related, mainly in 0.25 mg/kg grp.

ANIMALS: Cats of random origin, 2.2-3.5 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.03-0.75 mg/kg/d in corn oil d 10-58 of pregnancy.

ROUTE AND SITE: Oral in gelatin capsules

CONTROL INFORMATION: Controls treated corn oil alone

DURATION OF EXPERIMENT: Sacr on d 59 of pregnancy

EXAM. TYPE: Teratological

336

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Khera, K.S., Iverson, F., Hierlihy, L., Tanner, R. and Trivett, G. Teratology 10:69-76, 1974.

OBSERVED NEUROTOXIC EFFECTS: Clinical: 0.5 mg/d and over, ataxia, visual, sensory and righting-reflex losses. High brain levels of mercury. Cerebral degeneration, especially in white matter of cortex and internal granular layer of cerebellum.

ANIMALS: Cats, age 4-9 d

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.25-1.0 mg/kg dissolved in 0.05%, $NaHCO_3$, daily, up to 184 d.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Control treatment vehicle only

DURATION OF EXPERIMENT: Maximum 184 d.

EXAM. TYPE: Biochemistry, histology

COMPOUND: Mercury, chloromethyl-

000115093

REFERENCE: Ware, R.A., Chang, L.W. and Burkholder, P.M. Acta Neuropath 30:211-224, 1974.

OBSERVED NEUROTOXIC EFFECTS: Ultrastructure damage and subsequent dysfunction of blood-brain barrier induced 4-6 hr after administration. Horseradish peroxidase demonstrated: tracer extravasation into brain parenchyma after 4 hr and, tracer permeation into neurons and axons after 10-12 hr.

ANIMALS: 72 Rats, S-D, M, adult, av 200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 mg/kg, followed 10 min prior to sacr by Horseradish peroxidase: 10 mg in 0.25 ml saline, i.v.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 18 rats, 1 ml saline as controls.

DURATION OF EXPERIMENT: Serial sacr 0.5-24 hr.

EXAM. TYPE: Histochemistry, Histology

COMPOUND: Mercury, chlorophenyl

000100561

REFERENCE: Takeda, Y., Kunugi, T., Hoshino, O. and Ukita, T.
Tox. Appl. Pharm. 13: 156-164, 1968.

OBSERVED NEUROTOXIC EFFECTS: Alkyl mercury compounds excreted more slowly than inorganic or aryl compounds. Metabolism varied with C-chain length. Distribution in brain and reported neurotoxicity were related to structure of compound.

ANIMALS: Rats, Donryu, aged 7 wk

PREPARATION AND DOSE
or HISTORY OF PATIENT: Compounds labeled with ^{203}Hg; mercuric chloride 3 mg/kg, others 10 mg/kg (one dose).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial 1-8 d

EXAM. TYPE: Biochemistry

337

COMPOUND: Mercury, (3-cyanoguanidino)methyl-
000502396

REFERENCE: Cavanagh, J.B. and Chen, F.C.K.
Acta Neuropath. 19:208-215, 1971.

OBSERVED NEUROTOXIC EFFECTS: Early loss of hindlimb control, recovery complete 5 wk after stopping doses (5 mg/kg). Gross ataxia of all limbs at 14-16 d, recovery always incomplete, some died (7.5 mg/kg). By 10th-12th d Wallerian degeneration in peripheral nerves, then spinal ganglion cells, then axonal degeneration in cord, then discrete degeneration in cerebellum (Purkinje cells normal, no other brain findings).

ANIMALS: Rats, WAG/C, S-D, and Porton, M and F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.25 mg/ml, in 50% polyethyleneglycol 400
(1) 5 mg/kg/d for 8 d.
(2) 7.5 mg/kg/d for 8 d.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: "Many months"

EXAM. TYPE: Histology, behavior

338

COMPOUND: Mercury, (3-cyanoguanidino)methyl-
000502396

REFERENCE: Diamond, S.S. and Sleight, S.D.
Tox. Appl. Pharm. 23:197-207, 1972.

OBSERVED NEUROTOXIC EFFECTS: Demyelination of sciatic nerve, atrophy of cerebellum granular cells, Neuronal degeneration in cerebrum, hippocampus and cervical spinal cord. Peripheral nervous system and cerebellum lesions.

ANIMALS: 84 Rats, S-D, M, 100g

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.5-25.0 mg/100 g bw, single dose.
(2) 20 rats given LD_{50}, 1.335 mg/100 g bw.
(3) 1.0 mg/100 g bw, 1/wk.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: (2) 6 rats distilled water

DURATION OF EXPERIMENT: (1) 1 wk,

EXAM. TYPE: Clinical, histology

COMPOUND: Mercury, (3-cyanoguanidino) methyl-
000502396

REFERENCE: Magos, L. and Butler, W.H.
Fd. Cosmet. Toxicol. 10: 513-517, 1972.

OBSERVED NEUROTOXIC EFFECTS: Dose-time-related linear accumulation of methyl mercury in the brain. Granular-layer necrosis was observed in the cerebellum with white-matter edema. Ataxia was apparent.

ANIMALS: Rats, Porton, F, 200 g

PREPARATION AND DOSE or HISTORY OF PATIENT:
0.84 mg Hg/kg/d, 5 d/wk for up to 59 doses
1.68 mg Hg/kg/d, 5 d/wk for up to 34 doses
3.36 mg Hg/kg/d, 5 d/wk for up to 16 doses

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Sacrificed after last dose if surviving

EXAM. TYPE: Behavior, histology, chemistry

COMPOUND: Mercury, (3-cyanoguanidino) methyl-
000502396

REFERENCE: Spyker, J.M.
Federation Proc. 34:1835-1844, 1975.

OBSERVED NEUROTOXIC EFFECTS: Offspring of 6 mo-yr whose mothers were exposed to 8 mg/kg displayed tremors, ataxia, difficulty righting. Those of mothers exposed to a smaller dose underwent retarded growth and development. Mothers unaffected.

ANIMALS: Mice, Strain 129/SvSl: nulliparous, F, offspring

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5-8 mg/kg in saline.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Females with saline gave birth to offspring which developed normally.

DURATION OF EXPERIMENT: 1 yr.

EXAM. TYPE: Behavior, neurochemical analysis

336

COMPOUND: Mercury, cysteinylethyl-

REFERENCE: Mukai, N.
Acta Neuropath. 22:102-109, 1972.

OBSERVED NEUROTOXIC EFFECTS: Accretion in central nervous; predicatable selective necrosis of small granular neurons in koniocortex and neostriatum. Astroglial cell compartment believed to transport mercury protein complex into neurons.

ANIMALS: Mice: 24 C3H and 27 CD-1, 20-25 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.3 mg/d in 0.5 ml saline x 8 d, labeled with tritium.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 15 d

EXAM. TYPE: Histology, autoradiography

340

COMPOUND: Mercury, ((2,3-dihydroxypropyl)thio)methyl-

REFERENCE: Charlton, K.M.
Can. J. Comp. Med. 38:75-81, Jan. 1974.

OBSERVED NEUROTOXIC EFFECTS: Gait disturbance. Peripheral nervous system: Wallerian degeneration in sensory fibers and neuronal degeneration in dorsal root ganglia. Lesions caused by neuronal-axonal degeneration. Central nervous system: ischemic neuronal degeneration glial degeneration, and gliosis.

ANIMALS: 20 Pigs, Yorkshire, 7 M and 13 F, 10 wk old.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.24-5.76 mg Hg/kg/d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 untreated controls.

DURATION OF EXPERIMENT: 2 sacr at 1 d, others left to die.

EXAM. TYPE: Histology, necropsy.

COMPOUND: Mercury, hydroxymethyl-
001184572

REFERENCE: Berlin, M., Grant, C.A., Hellberg, J. and Schütz, A.
Arch. Env. Hlth. 30:340-348, 1975.

OBSERVED NEUROTOXIC EFFECTS: Operant behavior tests, filmed. As blood mercury was increased, sudden visual disorder was seen, suggesting tissue threshold for mercury toxicity. Typical cerebral cortical lesions always involved visual cortex, and the tissue methylmercury level was claimed to be the lowest associated with such lesions yet seen.

ANIMALS: Squirrel monkeys, M and F, 500-1000 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.2-0.8 mg/monkey/wk, adjusted to produce desired level in blood; 4 levels apparently aimed at (0.6-1.8 mcg/g); in some expts labeled methylmercury given.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Approx 9 mo.

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Mercury, hydroxymethyl-
001184572

REFERENCE: Falk, S.A., Klein, R., Haseman, J.K., Sanders, G.M., Talley F.A. and Lim, D.J.
Arch. Path. 97:297-305, 1974.

OBSERVED NEUROTOXIC EFFECTS: Only wt. loss, lethargy clinically; slow increase of brain mercury; pyknotic neurons in cerebellum.

ANIMALS: Guinea-pigs, Hartley, M, 250-300 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg/kg/d, 5 d/wk, for 1-6 wk

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Littermates, total 55, no details.

DURATION OF EXPERIMENT: Serial sacr to 11 wk.

EXAM. TYPE: Clinical, biochemical, histology

341<

COMPOUND: Mercury, hydroxymethyl-
001184572

REFERENCE: Herman, S.P., Klein, R., Talley, F.A. and Krigman, M.R.
Lab. Invest. 28(1):104-118, 1973.

OBSERVED NEUROTOXIC EFFECTS: Ataxic hindlimb gait, selective Wallerian-like degeneration in sensory fibers in dorsal root, sciatic nerve, brachial plexus and sural nerve. Sensory polyneuropathy in peripheral nerves, spinal ganglia and cord. Wallerian degeneration in peripheral sensory axons and central nervous system neuronal necrosis.

ANIMALS: 16 Rats, albino, C-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg Hg/kg/d, 5 d/wk for 1-3 wk.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 6 Rats treated sterile water.

DURATION OF EXPERIMENT: Sacr 1-24 d

EXAM. TYPE: Ultrastructural, histology, clinical

342<

COMPOUND: Mercury, hydroxymethyl-
001184572

REFERENCE: Null, D.H., Gartside, P.S. and Wei, E.
Life Sci. 12(2):65-72, 1973.

OBSERVED NEUROTOXIC EFFECTS: Mercury conc in fetal brains "at least twice" that in dams or nonpregnant adults. Interpreted by authors to explain greater susceptibility of fetus to compound.

ANIMALS: 20 Rats, F, 200-220 g, pregnant and non-pregnant.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5-40 mg Hg/kg to pregnant (d 13 gestation) and non-pregnant rats. Preliminary tests showed highest mercury concentration in brain found 5-9 d after treatment.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Control: saline only.

DURATION OF EXPERIMENT: 7 d after treatment

EXAM. TYPE: Chemistry

COMPOUND: Mercury, mercaptomethyl-

REFERENCE: Miyakawa, T., Deshimaru, M., Sumiyoshi, S., Teraoka, A., Udo, N., Hattori, E. and Tatetsu, S.
Acta Neuropath. 15:45-55, 1970.

OBSERVED NEUROTOXIC EFFECTS: Pathological changes in peripheral sensory nerve fibers: swelling and degeneration of Schwann cells; changes in both myelin sheaths and axons (beginning at nodes of Ranvier).

ANIMALS: Rats, adult, M, 100-115 g, 4 x 3 (rats & groups)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 mg/rat/d

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 Rats

DURATION OF EXPERIMENT: Sacrifice on d 4, 8, 12, 20.

EXAM. TYPE: Histology

COMPOUND: Mercury, mercaptomethyl-

REFERENCE: Mikayawa, T., Deshimaru, M., Sumiyoshi, S., Teraoka, A. and Tatetsu, S. Acta Neuropath. 17:6-13, 1971.

OBSERVED NEUROTOXIC EFFECTS: Day 7: Mitosis of Schwann cells. Day 250: Decreased number of myelinated fibers; some regeneration (peripheral nervous system). Posterior nerve root ganglion cells intact.

ANIMALS: 6 Rats, adult, M, 100-115 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/rat/d for 20 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 2 Rats

DURATION OF EXPERIMENT: 3 Rats sacrificed 7 d after last dose, 3 sacrificed 250 d afterwards. 1 rat/gp control.

EXAM. TYPE: Histology

3343

COMPOUND: Mercury, methyl-

REFERENCE: Abe, T., Haga, T. and Kurokawa, M. Brain Res. 86:504-508, 1975.

OBSERVED NEUROTOXIC EFFECTS: Blockage of axoplasmic transport. Depolymerized cerebral microtubules in vitro.

ANIMALS: Frogs, R. catesbeiana

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 5 mcl of 5mM methyl mercury 2 hr after labeled leucine. (2) 108.5 mcM to purified microtubule protein from pig brain.

ROUTE AND SITE: Inj., 9th dorsal root ganglion; In vitro

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: 38 hr.

EXAM. TYPE: Biochemistry

344

COMPOUND: Mercury, methyl-

REFERENCE: Albanus, L., Frankenberg, L., Grant, C., von Haartman, U., Jernelov, A., Nordberg, G., Rydalv, M., Schutz, A. and Skerfving, S. Env. Res. 5:425-442, 1972.

OBSERVED NEUROTOXIC EFFECTS: Gait and visual field impairment, convulsions. Over 90% of mercury was absorbed, 20% found in hair, 1% of remainder in brain (18 mcg/kg, all as methyl-mercury, comparable with compound as administered in lab experiments.

ANIMALS: Pike (Esox lucius) from contaminated and uncontaminated waters; Cats, European short-haired, 9 F and 6 M in 3 grps of 3 F and 2 M.

PREPARATION AND DOSE or HISTORY OF PATIENT: The pike were fed to the cats. Contaminated fish had been exposed to phenyl mercury acetate. Trace amounts of methylmercury hydroxide sprayed on homogenized contaminated and uncontaminated fish. Amount added corresponded to 0.6% of mercury present originally.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Noncontaminated fish, homogenized and frozen without further treatment.

DURATION OF EXPERIMENT: Up to 82 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Mercury, methyl-

REFERENCE: Fox, H.H., Patel-Mandlik, K. and Cohen, M.M. J. Neurochem. 24:757-762, 1975.

OBSERVED NEUROTOXIC EFFECTS: Decreased oxygen uptake and carbon dioxide production, increased production of pyruvate and lactate. Authors propose inhibition of tricarboxylic acid cycle as basis of organomercury neurotoxicity.

ANIMALS: Guinea-pig brain slices in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.01-0.5 mM in medium

ROUTE AND SITE: In vitro incubation

CONTROL INFORMATION: Mercury-free medium used for control.

DURATION OF EXPERIMENT: 1 hr in some cases.

EXAM. TYPE: Biochemistry

COMPOUND: Mercury, methyl-

REFERENCE: Ganther, H.E., Goudie, C., Sunde, M.L., Kopecky, M.J., Wagner, P., Oh, S-H. and Hoekstra, W.G.
Science 175:1122-1124, 1972.

OBSERVED NEUROTOXIC EFFECTS: Death rate from mercury diminished by selenium in amounts reported.

ANIMALS: 360 Japanese quail (Coturnix coturnix japonica), day-old, in 8 grps of 45.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0-20 ppm Hg as methylmercury in diets (various) with/without natural Se or Se supplement 0.5 ppm as Na_2SeO_3.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Yes

DURATION OF EXPERIMENT: Serial sacr to 7 wk

EXAM. TYPE: Epidemiology, behavior

345

COMPOUND: Mercury, methyl-

REFERENCE: Iwata, H., Okamoto, H. and Ohsawa, Y.
Res. Comm. Chem. Path. Pharm. 5(3):673-680, 1973.

OBSERVED NEUROTOXIC EFFECTS: A dose of 0.5 mg/kg sodium selenite given S.C. with the compound increased immediate accumulation of mercury in the brain but not in other organs; after 1 wk this accumulation was decreased. The authors concluded that selenium complexing with mercury hastened excretion of mercury.

ANIMALS: Rats, Wistar, M, 140-160 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 10 mg/kg/d 8-10 d

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 24 hr or 1 wk

EXAM. TYPE: Behavior, mortality, biochemistry

346

COMPOUND: Mercury, methyl-

REFERENCE: Klein, R., Herman, S.P. Brubaker, P.E., Lucier, G.W. and Krigman, M.R.
Arch. Path. 93:408-418, 1972.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, hindlimb-crossing; advanced peripheral neuropathy, vacuoles and neurophagia in anterior horns, fewer neurons in parts of brainstem, pyknotic nuclei in internal granular layer of cerebellum.

ANIMALS: Rats, Charles River, M, 280-365 g, total 28 in 4 grps

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 6 rats, 20 mg/kg in 2 doses 1/d, killed on d 3.
(2) 6 rats, 50 mg/kg in 5 doses 1/d, killed on d 6.
(3) 6 rats, 70 mg/kg in 7 doses 1/d, killed on d 8.
(4) 10 rats, 70 mg/kg in 7 doses 1/d, killed on d 15.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 26 in 4 grps, paired with above.

DURATION OF EXPERIMENT: Serial sacr to 15 d

EXAM. TYPE: Behavior, histology

COMPOUND: Mercury, methyl-

REFERENCE: Matsumoto, H., Koya, G. and Takeuchi, T.
J. Neuropath. Exp. Neurol. 24(4):563-574, 1965.

OBSERVED NEUROTOXIC EFFECTS: Small brains (650 g vs normal 960 g at 2.5 yr; 630 g vs 1125 g normal at 6 yr. Disorganized cellular structure of cortex, no active demyleination but poor corpora callosa, atrophy of cerebellum; no great changes in brain stem, few in cord, retina intact. However, pyramidal tracts were demyelinated, in brain and cord. Picture claimed typical of Minamata disease.

ANIMALS: 2 Human autopsies

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 F human children inferred to have been exposed in utero. Autopsy findings at 2.5 and 6 yr respectively. Families had histories of Minamata disease, no exposure of subjects.

ROUTE AND SITE: Transplacental

CONTROL INFORMATION: None

DURATION OF EXPERIMENT:

EXAM. TYPE: Histopathology

COMPOUND: Mercury, methyl-

REFERENCE: Rustam, H. and Hamdi, T.
Brain 97:499-510, 1974.

OBSERVED NEUROTOXIC EFFECTS: Multiple system involvement in most cases, severity varied within families. In coordination, ataxic gait, dysarthria and nystagmus. Reduced visual acuity, blindness and some speech disturbance. Sensory changes like peripheral neuropathy were not confirmed electrophysiologically.

ANIMALS: 53 Humans, 30 F, 23 M, 5-60 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Consumption of bread made from wheat treated with compound. Grain eaten within 1-3 mo, and 2-8 wk intervened between last poisoned meal and onset of symptoms. Patients selected from 6,530 admitted to hospital.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Cases occured between 1956-1962.

EXAM. TYPE: Clinical, physiological, clinical laboratory.

347

COMPOUND: Mercury, methyl-

REFERENCE: Rustam, H., Von Burg, R., Amin-Zaki, L. and El Hassani, S.
Arch. Env. Hlth. 30:190-195, 1975.

OBSERVED NEUROTOXIC EFFECTS: Selective muscle weakness was uncovered; neostigmine produced clinical improvement that was transient, suggesting direct/indirect action of methyl mercury on transmitter release.

ANIMALS: Human: 3 cases (F 25, M 10, F 10) from the 1972 outbreak with delayed recovery.

PREPARATION AND DOSE or HISTORY OF PATIENT: Effects of neostigmine therapy on electromyography were tested. 0.25-0.5 mg neostigmine and 0.3-0.6 mg atropine sulfate were given.

ROUTE AND SITE: I.M.

CONTROL INFORMATION: Alternate drug and placebo periods in each case.

DURATION OF EXPERIMENT: Months

EXAM. TYPE: Electrophysiology, behavior

348

COMPOUND: Mercury, methyl-

REFERENCE: Salvaterra, P., Lown, B., Morganti, J. and Massaro, E.J.
Acta Pharmacol. Toxicol. 33: 177-190, 1973.

OBSERVED NEUROTOXIC EFFECTS: Open field tests and alterations of selected glycolytic pathway intermediates corresponded and were dose-related, at 1 and 3 hr after doses; by 72 hr all normal.

ANIMALS: Mice, Swiss-Webster, M, 25-32 g, 6/grp.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1, 5, 10 mg Hg/kg as chloride salt. (2) 10 mg Hg/kg (single doses).

ROUTE AND SITE: I.P.

CONTROL INFORMATION: NaCl treated controls.

DURATION OF EXPERIMENT: (1) Serial sacr to 74 hr. (2) Serial sacr to 7 d.

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Mercury, methyl-

REFERENCE: Somjen, G.G., Herman, S.P., Klein, R. and Krigman, M.R.
Env. Hlth. Persp. 4:99, 1973. (Abstract).

OBSERVED NEUROTOXIC EFFECTS: Sensory neurons of dorsal root ganglia damaged first and most, accumulate methyl mercury more avidly. Neurons held more mercury than glia, satellite cells or Schwann cells.

ANIMALS: Rats

PREPARATION AND DOSE or HISTORY OF PATIENT: ns.

ROUTE AND SITE: ns.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, electrophysiology, radiosotope studies

COMPOUND: Mercury, methyl(methylthio)-

REFERENCE: Miyakawa, T., Sumiyoshi, S. and Deshimaru, M. Acta Neuropath. 30:33-41, 1974.

OBSERVED NEUROTOXIC EFFECTS: Destruction of myelin sheath, slight ataxia in hindlimbs, slight involvement of dorsal root ganglia fibers, morphological changes in nodes of Ranvier axons and Wallerian or segmental degeneration of nerve fibers. Involvement of the sural nerve.

ANIMALS: 10 Rats, Wistar, M, 100-110 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg/d x 10.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 5 control rats

DURATION OF EXPERIMENT: Sacr 600 d

EXAM. TYPE: Ultrastructural, histology

COMPOUND: Mercury, Methyl(thioacetamido)-

REFERENCE: Okinaka, S., Yoshikawa, M., Mozai, T., Mizuno, Y., Terao, T., Watanabe, H., Ogihara, K., Hirai, S., Yoshino, Y., Inose, T., Anzai, S. and Tsuda, M. Neurology 14: 69-76, 1964.

OBSERVED NEUROTOXIC EFFECTS: Clinical effects: numbness, speech disturbances, ataxia, paralysis, restriction of visual fields. Levels of Hg in blood, hair, liver, kidney, brain increased up to 40-fold. Widespread denervation of cerebral cortex granular layers, especially calcarine and superior temporal convolution, in cerebellar cortex (layer adjacent to Purkinje cells, but not Golgi cells), and in anterior horn of cord.

ANIMALS: Human: 3 cases, M, 17-35

PREPARATION AND DOSE or HISTORY OF PATIENT: Skin application for widespread fungal infection

ROUTE AND SITE: Topical, limbs and trunk

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 2 mo (fatal cases), 8 mo (surviving case)

EXAM. TYPE: Autopsy (histology), clinical

350

COMPOUND: Mercury, methyl (thioacetamido)-

REFERENCE: Yoshino, Y., Mozai, T. and Nakao, K.
J. Neurochem. 13: 397-406, 1966.

OBSERVED NEUROTOXIC EFFECTS: (1) The highest mercury level and the greatest histological changes occurred in the calcarine area.
(2) Almost all label was found in the protein fraction of the brain; little in the lipid or nucleic acid fractions. Subcellular distribution: mitochondrias > microsomes > supernatant. A lag time was noted from peak concentrations to onset of nervous symptoms.

ANIMALS: (1) Dogs, adult, 6.1-16 kg
(2) Rats, Wistar, 120 g

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 30-60 mg/kg
(2) ns (^{203}Hg)

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Dogs: 2-19 d
Rats: 48 hr or 6hr to 16 d

EXAM. TYPE: Histology, biochemistry

COMPOUND: Mercury, methyl (thioacetamido)-

REFERENCE: Yoshino, Y., Mozai, T. and Nakao, K.
J. Neurochem. 13: 1223-1230, 1966.

OBSERVED NEUROTOXIC EFFECTS: Protein synthesis in brain cortex slices was markedly inhibited before the onset of neurological signs; oxygen consumption, glycolysis, and sulfhydryl-enzyme activities were unchanged. After the onset of neurological signs, oxygen and aerobic glycolysis decreased. At advanced stages, activity of succinate dehydrogenase decreased. Thus, the compound exerted selective inhibition of enzyme synthesis.

ANIMALS: Rats, Wistar, M, 120 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 75 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Untreated.

DURATION OF EXPERIMENT: Up to 5-7 d

EXAM. TYPE: Biochemistry in vitro

COMPOUND: Methane, bromo-
000074839

REFERENCE: Collins, R.P.
California Med. 103: 112-116, 1965.

OBSERVED NEUROTOXIC EFFECTS: Exposure caused progressive sensorimotor weakness of the fingers and toes. Nine months after exposure ceased, a slight residual weakness of muscles persisted.

ANIMALS: Human: 1 case, M, 22, a fumigator

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposures possible over 18 mo before medical consultation and progressed for 4 mo until exposure ceased

ROUTE AND SITE: Probably dermal

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 13 mo

EXAM. TYPE: Clinical

351

COMPOUND: Methane, bromo-
000074839

REFERENCE: Kantarjian, A.D., and Shaheen, A.S.
Neurology 13:1054-1058, 1963.

OBSERVED NEUROTOXIC EFFECTS: Numbness of extremeties, unsteadiness on walking, some with ataxia. Deep reflexes absent or sluggish.

ANIMALS: 8 humans, M, 18-43 years.

PREPARATION AND DOSE or HISTORY OF PATIENT: 6-8 hrs daily, 6 d/wk, for 3 mo., dose believed to be low.

ROUTE AND SITE: Exposure by date fumigation process.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 6-8 mo.

EXAM. TYPE: Behavioral, biochemistry

352

COMPOUND: Methane, chloro-

000074873

REFERENCE: Scharnweber, H.C., Spears, G.N. and Cowles, S.R.
J. Occup. Med. 16:112-113, 1974.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, disorientation, combativeness, lethargy, loss of short-term memory, blurred vision, stated to be nonspecific signs, with progression only in Central Nervous System. Recovery in 6 wk to 3 mo. Physical and neurologic examination and laboratory studies "usually completely normal."

ANIMALS: Human: 6 cases, M, 24-58 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Workers with foam plastics, exposed to 200-400 ppm for 2-3 wk or more before onset of symptoms (TLV is 100 ppm).

ROUTE AND SITE: Inhalation, possibly skin contact

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 wk to 3 mo. per case.

EXAM. TYPE: Clinical

COMPOUND: Methane, dichloro-

REFERENCE: Steward, R.D., Fisher, T.N., Hosko, M.J., Peterson, J.E., Baretta, E.D., and Dodd, H.C.
Arch. Env. Hlth. 25: 342-348, 1972.

OBSERVED NEUROTOXIC EFFECTS: Sustained elevation of carboxyhemoglobin in all subjects, altered Visual Evoked Responses and other Central Nervous System signs in 2 subjects.

ANIMALS: 11 Humans, healthy M, 23-43 yr old, nonsmokers

PREPARATION AND DOSE
or HISTORY OF PATIENT: 986 ppm in air for 2 hr.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Previous tests.

DURATION OF EXPERIMENT: 2 hr.

EXAM. TYPE: Biochemistry

COMPOUND: Methane, dichloro-

REFERENCE: Weiss, G.
Abstr. Hyg. 43: 1123, 1968, abstracting from
Zentbl. Arbmed. Arbschutz. 17: 282-285, 1967 (Ger.).

OBSERVED NEUROTOXIC EFFECTS: Disturbed cerebral functions and hallucinations (optic and acoustic) attributed to toxic encephalitis caused by the compound.

ANIMALS: Human: 1 case, a distiller of compound

PREPARATION AND DOSE
or HISTORY OF PATIENT: Vapor 900-3600 ppm in air, "several" hr/d for 3 yr before symptoms and then 2 yr more. Compound was 98-100% pure.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

353

COMPOUND: 4,7-Methanoindene, 1,4,5,6,7,8,8-heptachloro-3a, 4,7,7a-tetrahydro-

000076448

REFERENCE: Ryan, W.H. and Shankland, D.L.
Life Sci. 10(1):193-200, 1971.

OBSERVED NEUROTOXIC EFFECTS: Instability and block of activity in giant fibers; no direct action on axonal membrane. Exo-acetoxy analog of aldrin was nontoxic. DDT with other compounds produced effects not seen with any compound alone.

ANIMALS: Cockroach (Periplaneta americana), surgically prepared
Housefiles, NAIDM strain

PREPARATION AND DOSE
or HISTORY OF PATIENT: DDT 10^{-4} M, other compounds (aldrin, dieldrin, endrin, heptachlor) 2×10^{-6} to 5×10^{-4} M (cockroaches). Up to 300 mcg/g (houseflies).

ROUTE AND SITE: Irrigation of exposed nerves (cockroaches), topical (houseflies)

CONTROL INFORMATION: Three types (described)

DURATION OF EXPERIMENT: Several hours

EXAM. TYPE: Electrophysiology

354

COMPOUND: 4,7-Methanoindene, 1,4,5,6,7,8,8-heptachloro-3a, 4,7,7a- tetrahydro- (heptachlor)
000076448

REFERENCE: St. Omer, V.
J. Neurochem. 18: 365-374, 1971.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, starting in some cases during injection. Intensity and other signs were directly related to increases of brain ammonia. Toxicity ranking: lindane > dieldrin > heptachlor > DDT. Brain glutamine increases resulting from conversion of ammonia to glutamine were related to the toxicity ranking, suggesting that the 4 compounds produced convulsions by one mechanism involving interference with the production and/or utilization of ammonia.

ANIMALS: Rats, adult F, Wistar, 250-300 g, surgically prepared.
Cockerels, White Leghorn or Barred Plymouth Rock, 12 wk, 1.4-1.6 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rats: mg/kg -- lindane 11.5, DDT 50, dieldrin 6, heptachlor 13.
Cockerels: mg/kg -- lindane 6.3, DDT 30, dieldrin 6, heptachlor 6.3.
The compounds stated to be structurally unrelated.

ROUTE AND SITE: Intra-arterial (carotid) at 1 ml/min

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: Up to 60 min, in controls 7 d

EXAM. TYPE: Behavior, biochemistry

COMPOUND: 4,7-Methanoisobenzofuran, 1,3,4,5,6,7,8,8-octachloro-1,3,3a,4,7,7a-hexahydro
000297789

REFERENCE: Worden, A.N.
Tox. Appl. Pharm. 14:556-573, 1969.

OBSERVED NEUROTOXIC EFFECTS: LD_{50} between 1.6 and 10 mg/kg for single oral dose, with central nervous system symptoms like those from other chlorinated hydrocarbons. Chronic toxicity for rats less than that of endrin or of 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo-5,8-endodimethanonaphthalene. Symptoms: twitching, frothing, opisthotonus, convulsions.

ANIMALS: Rats, Hooded Lister and S-D
Mice, Schofield
Guinea-pigs, albino
Hamsters, golden
Rabbits, Dutch
Cats, mongrel
Dogs, mongrel
Chickens, Light Sussex

PREPARATION AND DOSE or HISTORY OF PATIENT:
Acute: single dose by gavage to find LD_{50}
single dose S.C. (mice and rats, M and F, 10 each)
Chronic: dermal 2 mg/kg 1 dose to 0.3 mg/kg/d 30 d (rats, rabbits, guinea-pigs); 25-100 ppm in diet up to 78 d (rats), 5-30 ppm for 2 yr (rats), 0.025 and 0.1 mg/kg/d by gavage (dogs).

ROUTE AND SITE: Gavage, S.C. left flank.

CONTROL INFORMATION: Various including endrin equivalent

DURATION OF EXPERIMENT: Up to 2 yr.

EXAM. TYPE: Clinical, behavior, mortality, biochemistry

COMPOUND: Methanol
000067561

REFERENCE: Bennett, I.L., Jr., Cary, F.H., Mitchell, G.L., Jr. and Cooper, M.N. Medicine 32:431-463, 1953.

OBSERVED NEUROTOXIC EFFECTS: Cerebral edema, optic tracts ganglia degenerated but not optic nerves.

ANIMALS: Humans: 323 cases (308 Black, 15 White; 210 M, 113 F) ages 10-78 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Bootleg "whiskey" ingested in a 5-d period, October 1951, Atlanta, Ga. 90 gall distributed, 35-40% MeOH, under 4% EtOH in composition. Patients presented selves to hospitals.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 5 d

EXAM. TYPE: Clinical, autopsy (10 of 41 deaths)

355

COMPOUND: Methanol
000067561

REFERENCE: Erlanson, P., Fritz, H., Hagetam, K-E., Liljenberg, B., Tryding, N. and Voigt, G.
Acta Med. Scand. 177:393-408, 1965.

OBSERVED NEUROTOXIC EFFECTS: Acidosis, blindness, cerebral damage (massive necrosis). Hemorrhages into putamen. No reaction of glia. 4th case below: symmetrical slit-shaped cysts in putamina, residual damage; cerebellar loss of Purkinje cells could not be definitely attributed to the methanol.

ANIMALS: Human: 4 cases of accidental poisoning.

PREPARATION AND DOSE or HISTORY OF PATIENT: Accidental poisoning. All treated within 29-44 hr with alkali, ethanol, dialysis; 3 cases fatal, 4th died later; all were autopsied.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Up to 1.5 yr.

EXAM. TYPE: Behavior, chemistry, histology

356

COMPOUND: Methanol

000067561

REFERENCE: Guggenheim, M.A., Couch, J.R. and Weinberg, W.
Arch. Neurol. 24:550-554, 1971.

OBSERVED NEUROTOXIC EFFECTS: Immediate and permanent nervous system damage: bilateral optic atrophy, rigidity, spasticity, hypokinesia. Administration of levodopa improved condition.

ANIMALS: One Human, F, age 13 yr, 10 mo.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Ingestion of 90 and 240 ml antifreeze contg 60% methanol, no heavy metals, as suicide attempt.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Approx. 1 yr follow-up and therapy.

EXAM. TYPE: Hospital neurological exam.

COMPOUND: Methanol

000067561

REFERENCE: Riegel, H., and Wolf, G.
Food and Cosmet. Tox. 5:828-829, 1967.

OBSERVED NEUROTOXIC EFFECTS: Unconscious for 3 days, unable to swallow or speak. Eyesight permanently and severely damaged. Brain damage involving movement and walking disturbances still seen 20 years later. Symptoms similar to those of Parkinson's syndrome.

ANIMALS: 1 Human, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: Intake of "spirit" at a party.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Appears follow-up of 2 yr.

EXAM. TYPE: Clinical

COMPOUND: Methanol

000067561

REFERENCE: Roach, M.K., Davis. D.L., Pennington, W. and Nordyke, E.
Life Sci. 12(1):433-441, 1973.

OBSERVED NEUROTOXIC EFFECTS: Methanol inhibited active transport of probable neurotransmitters of the central nervous systems by synaptosomes. Authors conclude that alcohol interacts with membrane lipids of synaptosome.

ANIMALS: Rats, S-D, M, 200-250 g; brains removed and homogenates incubated in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: Graded amounts added to incubation medium; concentration not specified.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Control: incubation in medium with no alcohol.

DURATION OF EXPERIMENT: Laboratory procedure

EXAM. TYPE: Biochemistry.

3572

COMPOUND: 16-Methylpregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy

REFERENCE: Miyakawa, T., Sumiyoshi, S. and Deshimaru, M.
Acta Neuropath. 30:85-89, 1974.

OBSERVED NEUROTOXIC EFFECTS: Dose-related changes both groups: thalamus and hypothalamus vacuolar degeneration, hypertrophic mitochondria, astrocyte edema, more free ribosomes; Group (1) rats but not group (2) became restless.

ANIMALS: Rats, Wistar, M, 100-120 g

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 mg/kg for 30 d.
(2) 0.05 mg/kg for 130 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Controls mentioned, no details

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, histology

358

COMPOUND: 2-Methyoxyacridine, 6-chloro-9-[[4-(diethylamino)-1-methylbutyl]amino]-, dimethane sulfonate

REFERENCE: Smith, B.
J. Neurol. Neurosurg. Psychiat. 30: 506-510, 1967.

OBSERVED NEUROTOXIC EFFECTS: The myenteric plexus was examined, and histological changes were found. The author suggests her method for screening for neurotoxicity by looking for damage to the myenteric plexus in the large intestine.

ANIMALS: 45 Mice, TO, CFW and Porton strains, 20-25 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 3 mg/d for 5 d, 18 mice
Acute study: 10 mg I.P. or 2 mg I.V. one dose

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 2 d to 3 mo after last dose. Acute: 20 min.

EXAM. TYPE: Histology

COMPOUND: Morphinan-3,6-alpha-diol 17-allyl-7,8 didehydro-4,5-alpha-epoxy-, HCl

000062679

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha-epoxy-17-methyl-

000057272

REFERENCE: Davis, W.M. and Dhalsa, J.H.
Res. Comm. Chem. Path. Pharm. 6: 867-872, 1973.

OBSERVED NEUROTOXIC EFFECTS: Tropolone, which inhibits catecholamine-O-methyltransferase, reduced the morphine LD_{50} to 54 mg/kg. The authors concluded that the release of brain catecholamines was a strong factor in morphine toxicity.

ANIMALS: Rats, Holtzman, M, 350-450 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10-640 mg/kg; LD_{50} 292 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: The LD_{50} served as control for tests of modifying drugs

DURATION OF EXPERIMENT: Up to 24 hr.

EXAM. TYPE: Mortality

359

COMPOUND: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, hydrochloride, (5-alpha-6-alpha)-
000052266

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} >80 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

360

COMPOUND: Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha epoxy-17-methyl-, sulfate

000064313

REFERENCE: Ross, D.H., Medina, M.A. and Cardenas, H.L.
Science 186:63-65, 1974.

OBSERVED NEUROTOXIC EFFECTS: Regional Ca depletion (from 55-60 to 33-39 mcg/g) in hypothalamus, hippocampus, corpus striatum, and cortex; antagonized by naloxone. Ca considered important in release of transmitters and neuron stimulation.

ANIMALS: Rats, S-D, M, 150-200 g, groups of 3

PREPARATION AND DOSE or HISTORY OF PATIENT: Morphine sulfate 25 mg/kg, 30 min antemortem
Ethanol 1.5 mg/kg 120 min antemortem
Other treatments also given.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Untreated, 1:1, each expt replicated 3 or more times

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha epoxy-17-methyl-, sulfate

000064313

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-20 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Morphinan-6-one, 4-5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5-alpha)-

000357084

REFERENCE: Tseng, L.F., Menon, M.K. and Loh, H.H.
Neuropharmacology 14: 247-250, 1975.

OBSERVED NEUROTOXIC EFFECTS: Naloxone precipitated abstinence signs, teeth chattering, myoclonic twitch, and repetitive shaking. Bilateral transverse lesions suggested that the different signs originated in different brain areas.

ANIMALS: Rats, S-D, M, 350-400 g, morphine-dependent and surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 4 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Sham-operated rats

DURATION OF EXPERIMENT: 30 min each test

EXAM. TYPE: Behavior

361

COMPOUND: Morpholine, 2-chloroethyl-, hydrochloride

REFERENCE: Goldin, A., Now, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B.
J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic β-chloroethylamines but not when (a) OH or bromine replaced the β chlorine, (b) a β-phenyl group replaced one of the β hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary β-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-β-chloroethylamines. Piperidine and morpholine analogs and arsacetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

362

COMPOUND: Morpholinium, 2,2'-(4,4'-biphenylylene)bis(2-hydroxy-4,4-dimethyl-, dibromide)

REFERENCE: Shellenberger, M.K. and Domino, E.F.
Int. J. Neuropharmacol. 6: 283-291, 1967.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced seizures with a 20 min latency. The authors inferred that the compound exerted direct action on possible cholinergic receptors, rather than acting by way of acetylcholinesterase inhibition.

ANIMALS: Dogs, beagle-like mongrel, M and F, 8-12 kg, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg (basis not given)

ROUTE AND SITE: Intraventricular

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: At peak response, duration ns

EXAM. TYPE: EEG, biochemistry

COMPOUND: Mytilus edulis toxins

REFERENCE: Evans, M.H.
Br. J. Pharmac. 40: 847-865, 1970.

OBSERVED NEUROTOXIC EFFECTS: Outbreak of paralytic poisoning in about 80 subjects in NW England in May, 1968. Assays and signs in animals and nerve preparations were used to try to identify the toxins.

ANIMALS: Humans: about 80 who suffered paralytic shellfish poisoning
Mice, rabbits, and desheathed sciatic nerves from rat, frog and newt, and rat cauda equina nerves.

PREPARATION AND DOSE or HISTORY OF PATIENT: Humans: unwitting ingestion.
Animals and in vitro preparations: assay of crude extracts and part-purified toxins.

ROUTE AND SITE: Various

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, chemistry

COMPOUND: Naphthalene methanol, alpha-(isopropylamino) methyl-, hydrochloride

001722516

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >40 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

363

COMPOUND: Napthalimide, N-hydroxy-,diethyl phosphate

001491414

REFERENCE: Sherman, M., Herrick, R.B., Rose, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 43.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

364
A

COMPOUND: Neomycin
001404042

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: (1) Depressed neuromuscular transmission of doses of 25 and 50 mg/kg. (2) Immediate ataxia in chicks.

ANIMALS: (1) 6 Rabbits
(2) Chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 25 mg/kg followed by 50 mg/kg, in saline.
(2) 50-100 mg/kg

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, behavior

COMPOUND: Nickel
007440020

REFERENCE: Prakash, N.J., Fontana, J. and Henkin, R.I.
Life Sci. 12(1):249-259, 1973.

OBSERVED NEUROTOXIC EFFECTS: Inhibited ($Na^+ + K^+$) ATPase, although never more than 20%, even at 0.2 mM. Inhibition involved blockage of norepinephrine and choline uptake.

ANIMALS: Rat brain synaptosomes in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Ni^{++} chloride added to medium in various expts.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: Minutes

EXAM. TYPE: Biochemistry

COMPOUND: Nitrous acid, pentyl ester

000463047

REFERENCE: Dewey, W.L., Tucker, L.S., Prange, A., Spaulding, T. and Chau, T.T. Res. Comm. Chem. Path. Pharm. 5(3):889-892, 1973.

OBSERVED NEUROTOXIC EFFECTS: Inhalation: tremors, ataxia, short duration. I.V.: generalized convulsion in 30 sec, died in 1 min. Vomiting, defecation and other "unpleasant" effects reported.

ANIMALS: Mice for LD_{50} studies
Dogs, 5-10.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Various doses, I.V. or by inhalation (dogs)

ROUTE AND SITE: I.V., inhalation

CONTROL INFORMATION: No controls

DURATION OF EXPERIMENT: 1 d

EXAM. TYPE: Behavior

365

COMPOUND: 2,Norbornene, 1,2,3,4,7,7-hexachloro-5,6-bis(chloromethyl)-

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y. Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions. Acute: No mortality at highest dose level (5000 mg/kg), and no signs of intoxication.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} > 5000 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

366

COMPOUND: Notechis scutatus scutatus venom

REFERENCE: Datyner, M.E. and Gage, P.W.
Br. J. Pharmac. 49: 340-354, 1973.

OBSERVED NEUROTOXIC EFFECTS: 50 mcg/ml blocked elicited twitches without affecting compound action potentials. 1-10 mcg/ml reduced amplitude of endplate potentials and inhibited depolarizations by carbachol. The authors concluded that a venom fraction was bound to acetylcholine. Other in vitro effects were observed.

ANIMALS: Isolated sciatic-sartorius nerve-muscle preparations from Queensland cane toads (Bufo marinus)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1-200 mcg/ml of Ringer solution

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Minutes to 6 hr

EXAM. TYPE: Electrophysiology

COMPOUND: Notechis scutatus scutatus venom, toxin from

REFERENCE: Harris, J.B., Karlsson, E. and Thesleff, S.
Brit. J. Pharmac. 47: 141-146, 1973.

OBSERVED NEUROTOXIC EFFECTS: The resting membrane potentials and action potentials were normal. There was a low frequency of miniature endplate potentials (amplitude unchanged). The toxin was almost ineffective in vitro. In vivo, administration caused deaths by respiratory paralysis.

ANIMALS: Mice, NMRI, M, 25-30 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mcg/mouse

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Various

EXAM. TYPE: In vitro studies on hemidiaphragm and digitorum longus nerve-muscle preparations dissected from mice intoxicated in vivo

COMPOUND: Organophosphate pesticides

REFERENCE: Rodnitzky, R.L., Levin, H.S., Mick, D.L.
Arch. Env. Hlth. 30:98-103, 1975.

OBSERVED NEUROTOXIC EFFECTS: Behavior tasks performed as well as by controls, blood ChE in normal range though lower in some subjects than control values. Conclusion: that "higher nervous system functions" have "relative resistance" to mild chronic exposures.

ANIMALS: 23 Humans (12 farmers, 11 commercial applicators)

PREPARATION AND DOSE or HISTORY OF PATIENT: Regularly used organophosphates, had applied them personally to at least 500 acres and who had used them in the previous 2 wk every working day.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: Age-education-matched farmers whose pesticides, if any, were applied for them by contractors.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior tasks, blood chemistry

3674

COMPOUND: Ouabain

000036066

REFERENCE: Doggett, N.S.
Life Sci. 12(1):121-129, 1973.

OBSERVED NEUROTOXIC EFFECTS: Hypothermia did not involve brain noradrenergic systems but possible direct action on thermoregulation including interference with amine function.

ANIMALS: Mice, TO, M, 16-20 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-0.25 mcg/mouse with one or more of: noradrenaline, phentolamine, α-methylmetatyrosine, (+)-amphetamine.

ROUTE AND SITE: Intracerebroventricular

CONTROL INFORMATION: Controls saline treated

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Biochemistry

368

COMPOUND: Ouabain

000036066

REFERENCE: Grasso, A. and Majori, G.
J. Econ. Entomol. 62: 944-945, 1969.

OBSERVED NEUROTOXIC EFFECTS: Ouabain is known to inhibit the Na^+/K^+-dependent ATPase found in the ventral nerve cord of cockroaches. By inference, such was presumed to be the basis of ouabain toxicity in the housefly.

ANIMALS: Houseflies (Musca domestica), adult, 22 mg

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50} found to be: Feeding 270-690 mg/kg
Topical 292-1600 mg/kg
Injected 0.9-2.25 mg/kg
Ranges of averages of three groups: susceptible to resistant.

ROUTE AND SITE: Injection into thorax; dermal to dorsal surface; feeding in sucrose by calibrated micropipet method.

CONTROL INFORMATION: Vehicles

DURATION OF EXPERIMENT: 24 hr

EXAM. TYPE: Count of knocked-down insects

COMPOUND: Ouabain

000036066

REFERENCE: Towfighi, J. and Gonatas, N.K.
Lab. Invest. 28:170-180, 1973.

OBSERVED NEUROTOXIC EFFECTS: Edema corresponding to spread of labeled more in adults than juveniles, central zone of swollen dendrites, Golgi, and rough endoplasmic reticulum, marginal zone of swollen astrocytes, presynaptic terminals, and dark neurons. Central zone interpreted as primary effect, marginal as secondary to pressure or ischemia.

ANIMALS: 129 Rats, Osborne-Mendel, M and F, adult and juvenile.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.0006-0.00125 mg/rat (1-5 d old); 0.0025 mg/rat (older); in buffered saline pH 7.2.

ROUTE AND SITE: Intracerebral

CONTROL INFORMATION: Vehicle only.

DURATION OF EXPERIMENT: 2 hr.

EXAM. TYPE: Histology, histochemistry

COMPOUND: Oxalic acid, bis(cyclohexylidenehydrazide)

000370810

REFERENCE: Carlton, W.W.
Life Sci 6:11-19, 1967.

OBSERVED NEUROTOXIC EFFECTS: Hydrocephalus and spongy degeneration of brain, cord and sciatic nerve. Copper reduced hydrocephalus but not edema, spongy degeneration or astrogliosis. Liability to hydrocephalus decreased with age. Myelin loss occurred late, spongy degeneration early, glial proliferation in-between.

ANIMALS: Mice, M, albino, weanling aged 21-28 d (groups of 10)

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5% in diet of Cuprizone precursors: cyclohexanone and oxaldihydrazide.
(2) 0.5% in diet, plus vitamins at 1000x the recommended requirements.
(3) 0.5% in diet, plus diuretic, Diurill, 0.5 and 1 gm/kg.
(4) 0.2% in diet, plus copper 130 and 260 ppm.
(5) 0.5% in diet for 8 wk.

ROUTE AND SITE: Oral

CONTROL INFORMATION: (3) Diurill treatment only

DURATION OF EXPERIMENT: Maximum 9 wk

EXAM. TYPE: Histology, hematology

369

COMPOUND: Oxalic acid, Bis(Cyclohexylidenehydrazide)

REFERENCE: Pattison, I.H., Clarke, M.C., Haig, D.A. and Jebbett, J.N.
Res. Vet. Sci. 12: 478-480, 1971.

OBSERVED NEUROTOXIC EFFECTS: Cultured brain cells from mice treated with the compound or with scrapie but not controls tended to adhere to glass.

ANIMALS: Mice, BSVS, aged 4-6 wk

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5% of diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated, treated with scrapie agent

DURATION OF EXPERIMENT: Over 16 d

EXAM. TYPE: Biophysics in vitro

370

COMPOUND: Oxalic acid, bis(cyclohexylidenehydrazide)

000370810

REFERENCE: Pattison, I.H. and Jebbett, J.N.
J. Path. 109:245-250, 1973.

OBSERVED NEUROTOXIC EFFECTS: Scrapie-like spongiform encephalopathy; functional recovery in "a few days," histological recovery in 34 d; apparent correlation with microglial proliferation.

ANIMALS: Mice, BSVS, F aged 3-6 wk, weaned.

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.5% in diet, up to 15 mg/mouse/d, for 7, 14, 21 d then 60 d untrtd.: 3 grps of 12 clinically abnormals.
(2) Similar test, adding 28 and 35 d trtmts.
(3) 37 d trtmt (max), 52 d no trtmt, 38 d (max) trtmt, and then 52 d no treatment.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr to 179 d

EXAM. TYPE: Histology, behavior

COMPOUND: Oxalic acid, bis(cyclohexylidenehydrazide)

000370810

REFERENCE: Suzuki, K. and Kikkawa, Y.
Am. J. Path. 54:307-325, 1969.

OBSERVED NEUROTOXIC EFFECTS: Inactive at 1-2 wk, hindlimb weakness, most died at 3 wk. Spongy degeneration in CNS: brainstem and cerebellar white matter. Vacuoles in myelin and glia.

ANIMALS: 30 Mice, Swiss-Webster, M

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5 g/100 g diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 10 untreated controls

DURATION OF EXPERIMENT: About 3 wk

EXAM. TYPE: Behavior, histology

COMPOUND:
Oxalic acid, dihydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.7 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

3714

COMPOUND: 2H-1,3,2-oxazaphosphorine, 2-(bis(2-chloroethyl)amino) tetrahydro-, 2-oxide

000050180

REFERENCE: Levine, S., and Sowinski, R.
J. Neuropath. Exp. Neurol 32(3), 365-370, 1973.

OBSERVED NEUROTOXIC EFFECTS: Lesions of the choroid plexus were well developed after 24-48 hours and were characterized by severe edema, hemorrhage, and focal leukocytic infiltration. Progressed to necrosis of individual villi and hemorrhage infarction of an entire plexus after 4-6 days. Plexitis was greatest in plexus of 4th ventricle.

ANIMALS: Rats, Lewis strain: (1) 38 rats, 100-300 g.
(2) 8 rats, 100-175 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 125-500 mg/kg in saline.

ROUTE AND SITE: S.C. or I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 7 d.

EXAM. TYPE: Histology

3125

COMPOUND: 2-Oxazolidinone, 5-((O-methoxyphenoxy)methyl)

000070075

REFERENCE: Benitz, K-F., Moraski, R., Roepke, R.R. and Wozniak, L.A.
Tox. Appl. Pharm. 4:220-237, 1962.

OBSERVED NEUROTOXIC EFFECTS: (1) Dogs, ataxia and emesis on 480 or 600 mg/kg/d.
(2) Rats, no neural signs.

ANIMALS: (1) 6 Dogs, beagle, 1 M and 1 F/group, 3 groups.
(2) 80 Rats, Sherman, 10 M and 10 F/group, 4 groups.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Short term - 70, 200, 600 mg/kg/d for 30 d.
Long term - 30, 120, 480 mg/kg/d for 6 mo.
(2) 0.0625, 0.25, 1% in diet.

ROUTE AND SITE: Oral (dogs and rats)

CONTROL INFORMATION: 1 Group untreated (dogs and rats)

DURATION OF EXPERIMENT: (1) 30 d and 6 mo.
(2) 30 d

EXAM. TYPE: Behavior, pathology (at sacrifice)

COMPOUND: 2-Oxazoline, 2-amino-5-phenyl-

002207503

REFERENCE: Borbely, F., Past, A. and Velvart, J.
Arch. Toxikol. 26:117-124, 1970.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, cramps, convulsions; transient.

ANIMALS: 30 human cases

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-2 mg/kg estimated as toxic for central nervous system.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 2 hr.

EXAM. TYPE: Clinical

COMPOUND: Oxygen

REFERENCE: Barnard, E.E.P.
Proc. Roy. Soc. Med. 64: 874-876, 1971.

OBSERVED NEUROTOXIC EFFECTS: Men: convulsions, susceptibility (threshold, taken as 1.7 atm) varied day-to-day. Mice: Time course of minor convulsions, slow onset, duration 5-10 sec; major convulsions, rapid onset, preceded by spinning, duration 30-60 sec followed by tonic spasm for 15-30 sec; normal movements then till next convulsion. Dose-response (atm) and major-minor relationships reported.

ANIMALS: Human: Naval volunteers
Mice: unspecified.

PREPARATION AND DOSE or HISTORY OF PATIENT: Diving experiments, no details
Mice: chamber experiments, no details

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

373

COMPOUND: Oxygen

REFERENCE: Joanny, P., Corriol, J. and Brue, F.
Science 167:1508-1510, 1970.

OBSERVED NEUROTOXIC EFFECTS: Less oxidation by tissues, fall of phosphocreatine and ATP, and rise of lipid peroxides. The increased lipid peroxides is attributed to the toxic effects of hyperbaric oxygen.

ANIMALS: Guinea-pig, brain cortex slices in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: Incubation in presence of 1-10 atm of pure O_2 and labeled substrates.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory methods

DURATION OF EXPERIMENT: 60 min

EXAM. TYPE: Biochemistry

COMPOUND: Oxygen

REFERENCE: Walter, D.C., Underwood, B.C. and Nelson, S.R.
Comp. Gen. Pharm. 5: 165-167, 1974.

OBSERVED NEUROTOXIC EFFECTS: Tremors, loss of righting reflex, 6 hr survival limit. The authors report much variation among species.

ANIMALS: Cockroach (Periplaneta americana), adult M & F

PREPARATION AND DOSE or HISTORY OF PATIENT: 6 atm (75 psi), 0-6 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Untreated

DURATION OF EXPERIMENT: Serial to 6 hr.

EXAM. TYPE: Behavior, physiology

COMPOUND: Oxygen

REFERENCE: Wood, J.D.
J. Neurochem. 17: 573-579, 1970.

OBSERVED NEUROTOXIC EFFECTS: Susceptibility to O_2 convulsions rose with age at exposure (1-23 d), and brain γ-aminobutyric acid (GABA) changed less with age. The rate of GABA depletion was related to the time of convulsions. Injected GABA protected young chicks more than old, consistent with decreasing permeability of blood-brain barrier to GABA with age.

ANIMALS: Cockerels, White Leghorn, age 1 d

PREPARATION AND DOSE or HISTORY OF PATIENT: O_2: exposure to 60 psi for 5-38 min
GABA: 1-20 mmoles/kg 30 min before exposure to O_2 or sacrifice

ROUTE AND SITE: O_2, inhalation; GABA, I.P.

CONTROL INFORMATION: One or other treatment omitted

DURATION OF EXPERIMENT: About 1 hr

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Ozone

010028156

REFERENCE: Kulle, T.J. and Cooper, G.P.
Arch. Env. Hlth 30:237-243, 1975.

OBSERVED NEUROTOXIC EFFECTS: Examined effects of prolonged exposure. Ozone increased response to amyl alcohol; perfusion with air for 1 hr. partly normalized the response.

ANIMALS: Rats, S-D, M, 250-400 g, surgically prepared for testing of nasopalatine nerve twigs.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 ppm for 1 hr. Repeated tests in many animals, for total exposure of 5 hr.

ROUTE AND SITE: Gas drawn through nasal cavities by vacuum pump.

CONTROL INFORMATION: Pre-exposure control responsiveness determined by test series of amyl alcohol (0.3, 0.7, 1.0, 3.3, 6.7, 10.0 pph) and then test repeated after exposure to test compound. Air controls also run.

DURATION OF EXPERIMENT: Several hr.

EXAM. TYPE: Electrophysiology

375

COMPOUND: Pentaborane (9)

019624227

REFERENCE: Feinsilver, L., Lawson, L.H., Yevich, P.P. and Jacobson, K.H.
U.S. Army CWL Report CWLR 2367, 1960.

OBSERVED NEUROTOXIC EFFECTS: LC_{50} under conditions were:
Rats - 6ppm; mice - 3ppm. Signs included ataxia; depression, prostration, tremors, clonic convulsions, interpreted as "marked effects upon" the central nervous system.

ANIMALS: Rats, ages 8-10 wk, M
Mice, 8-10 wk, F
Dogs, beagle, M.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposed to vapors of compounds in LC_{50} study, 2-4 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Observation to 7 d after exposure

EXAM. TYPE: Behavior, pathology

376

COMPOUND: Pentaborane (9)
019624227

REFERENCE: Schoettlin, C.E., Cianko, G.M., Walter, R.D. and Freedman, T. ASD Tech. Report 61-438 (USAF), 1961.

OBSERVED NEUROTOXIC EFFECTS: Mental confusion, lack of coordination; EEG changes reversible about 1 yr after exposure. One or more expsoures produced abnormalities. EEG's not specific for boranes.

ANIMALS: Humans: 119 rocket fuel handlers

PREPARATION AND DOSE or HISTORY OF PATIENT: Symptoms and signs recorded, plus a total 333 EEG's. Composition of fuels ns.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: 22 controls

DURATION OF EXPERIMENT: Over 1 yr

EXAM. TYPE: Behavior, EEG

COMPOUND: 2-Pentanone, 4-methyl-
000108101

REFERENCE: Spencer, P.S., Schaumburg, H.H., Raleigh, R.L. and Terhaar, C.J. Arch. Neurol. 32: 219-222, 1975.

OBSERVED NEUROTOXIC EFFECTS: Compound produced no clinical signs, no histological damage except in distal tibial and ulnar nerves, which were not degenerated.

ANIMALS: 6 Rats, young adult

PREPARATION AND DOSE or HISTORY OF PATIENT: 1,500 ppm commercial grade in air, exposed 6 hr/d, 5 d/wk for up to 5 mo. Approx. 3% MBK contaminant.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Normal control rats

DURATION OF EXPERIMENT: 5 mo.

EXAM. TYPE: Behavior, histology

COMPOUND: Pesticides (unspecified)

REFERENCE: Drenth, H.J., Ensberg, I.F.G., Roberts, D.V. & Wilson, A.
Arch. Env. Hlth. 25:395-398, 1972.

OBSERVED NEUROTOXIC EFFECTS: Abnormal electromyographic (EMG) exam in 40% indicating disturbed peripheral nervous system function. No abnormal blood cholinesterase or other biological data.

ANIMALS: Human: 102 agric. workers with pesticides, M, aged 17-59.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure varied from 1 compound daily for 7 d to several compounds/d. Screening study for blood cholinesterase and EMG function.

ROUTE AND SITE: Skin, inhalation, oral

CONTROL INFORMATION: 130 industrial workers not exposed to pesticides

DURATION OF EXPERIMENT: 2 screenings 2 mo apart.

EXAM. TYPE: Electomyography, blood chemistry

377<

COMPOUND: Phenethylamine, p-chloro-alpha, alpha-dimethyl
000461789

REFERENCE: Lullmann-Rauch, R.
Acta Neuropath. (Berl)29: 237-249, 1974.

OBSERVED NEUROTOXIC EFFECTS: Significant ultrastructural alterations of nerve cells, both in spinal cord and in cerebellar cortex.

ANIMALS: Rats, Wistar, M., Young Adult.

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg b.w., 5d/wk in saline 0.5ml/100g bw, for 5 wk.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls inj. saline

DURATION OF EXPERIMENT: 5 wk

EXAM. TYPE: Histology

378

COMPOUND: Phenethylamine, 4-chloro-2-methyl-, DL-

REFERENCE: Harvey, J.A., McMaster, S.E. and Yunger, L.M. Science 187:841-843, 1975.

OBSERVED NEUROTOXIC EFFECTS: Dissolution of neurons in ventral midbrain tegmentum (B-9 serotonergic cell group) and in substantia nigra, starting at 1 d and progressing to 30 d. Damage interpreted to explain effects of compound on 5-HT and tryptophan-5-hydroxylase.

ANIMALS: 25 Rats, Holtzman, M, 150-200 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2.5-20 mg/kg in saline to 1 ml.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: Serial sacr to 30 d

EXAM. TYPE: Histology

COMPOUND: Phenethylamine, 4-chloro-alpha-methyl-

REFERENCE: Sanders-Bush, E., Bushing, J.A. and Sulser, F. Biochem. Pharmacol. 21:1501-1510, 1972.

OBSERVED NEUROTOXIC EFFECTS: Dose-related inhibition of tryptophan hydroxylase. Authors claim that this explains the prolonged reductions of 5-hydroxytrptamine and 5-hydroxy-indoleacetic acid produced by this compound.

ANIMALS: Rats, S-D, M, 180-220 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Pretreatment (some experiments) 2-10 mg/kg 16 hr before sacrifice (25 rats), in one expt 6 d.
In vitro: homogenized brainstems used to assay tryptophan hydroxylase activity with/without p-chloroamphetamine.

ROUTE AND SITE: Pretreatment: I.P.

CONTROL INFORMATION: Pretreatment: 5 rats no dose.

DURATION OF EXPERIMENT: Pretreatment 16 hr., or less, one expt. 6 d.

EXAM. TYPE: Biochemical

COMPOUND: Phenethylamine, 2-chloro-2-methyl-, (±)-

REFERENCE: Wong, D.T., Horng, J-S., and Fuller, R.W.
Biochem. Pharmacol. 22:311-322, 1973.

OBSERVED NEUROTOXIC EFFECTS: Synaptosomes accumulated serotonin by (a) high-affinity and (b) low-affinity processes. 2-chloroamphetamine inhibited both processes.

ANIMALS: Rat brain in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Synaptosomes isolated from homogenized whole brains, and uptake of labeled serotonin or norepinephin measured in presence/absence of the amphetamine. Some rats pretreated with the amphetamine.

ROUTE AND SITE: Addition to incubation medium

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: Pretreatment up to 22.5 hr; in vitro 5 sec to 30 min.

EXAM. TYPE: Biochemical

376

COMPOUND: Phenethylamine, 3-chloro-2-methyl-, (±)-

REFERENCE: Wong, D.T., Horng, J-S., and Fuller, R.W.
Biochem. Pharmacol. 22:311-322, 1973.

OBSERVED NEUROTOXIC EFFECTS: Synaptosomes accumulated serotonin by (a) high-affinity and (b) low-affinity processes. 3-chloroamphetamine inhibited both processes.

ANIMALS: Rat brain in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Synaptosomes insolated from homogenized whole brains, and uptake of labeled serotonin or norepinephin measured in presence/absence of the amphetamine. Some rats pretreated with the amphetamine.

ROUTE AND SITE: Addition to incubation medium.

CONTROL INFORMATION: Laboratory controls.

DURATION OF EXPERIMENT: Pretreatment up to 22.5 hr; in vitro 5 sec to 30 min.

EXAM. TYPE: Biochemical

380 A

COMPOUND: Phenethylamine, 4-chloro-2-methyl-, (±)-

REFERENCE: Wong, D.T., Horng, J-S., and Fuller, R.W.
Biochem. Pharmacol. 22:311-322, 1973.

OBSERVED NEUROTOXIC EFFECTS: Synaptosomes accumulated serotonin by (a) high-affinity and (b) low-affinity processes. 4-chloroamphetamine strongly inhibited (a) and inhibited (b) to a lesser extent.

ANIMALS: Rat brain in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Synaptosomes isolated from homogenized whole brains, and uptake of labeled serotonin or norepinephin measured in presence/absence of the amphetamine. Some rats pretreated with the amphetamine.

ROUTE AND SITE: Addition to incubation medium

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: Pretreatment up to 22.5 hr; in vitro 5 sec to 30 min.

EXAM. TYPE: Biochemical

COMPOUND: Phenethylamine, N-alpha-dimethyl-, hydrochloride, (-)-

REFERENCE: Kasirsky, G. and Tansy, M.F.
Teratology 4:131-134, 1971.

OBSERVED NEUROTOXIC EFFECTS: Both mice and rabbits showed excitement within 5 min after ttmt, continuing for 6-7 hr. Fetal anomalies: exencephaly, anophthalmia, microphthalmia greater in all treated litters of mice; exencephaly and microphthalmia in rabbits litters.

ANIMALS: Mice, CF1, pregnant; Rabbits, New Zealand white, F, pregnant and M, sires.

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: 5 or 10 mg/kg/d for 3, 4, or 7 d during d 9-15 of gestation.
Rabbits: 1.5 mg/kg for 4, 6, or 18 d during d 12-30 of gestation. Males: 1.5, 3.0, or 5.0 mg/kg/d for 3 mo. prior mating.

ROUTE AND SITE: I.V. Mice: tail, Rabbits: ear.

CONTROL INFORMATION: Untreated and saline ttd groups for mice and rabbits.

DURATION OF EXPERIMENT: Mice sacr day 19, Rabbits (F) sacr day 30.

EXAM. TYPE: Teratological

COMPOUND: Phenethylamine, N-alpha-dimethyl-, hydrochloride, (-)-

REFERENCE: Schuster, C.R., and Fischmann, M.W.
Federation Proceedings 34:1845-1451, 1975.

OBSERVED NEUROTOXIC EFFECTS: Dose of 9.0 and 5.0 mg/kg caused collapse with no sympathomimetic symptoms in contrast to the dose of 2.5 and 3.0 mg/kg which brought on piloerection, pupillary dilation, salvation, tremors in extremities.

ANIMALS: 19 Monkeys, Rhesus, M

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 ml I.V. over 10 sec. Dose range 9.0-1.0 mg/kg.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavioral

381

COMPOUND: Phenethylamine, alpha-methyl-(+)-amphetamine

REFERENCE: Wong, D.T., Horng, J-S., and Fuller, R.W.
Biochem. Pharmacol. 22:311-322, 1973.

OBSERVED NEUROTOXIC EFFECTS: Synaptosomes accumulated serotonin by (a) high-affinity and (b) low-affinity processes. Compound weakly inhibited both processes.

ANIMALS: Rat brain in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: Synaptosomes isolated from homogenized whole brains, and uptake of labeled serotonin or norepinephin measured in presence/absence of the amphetamine. Some rats pretreated with the amphetamine.

ROUTE AND SITE: Addition to incubation medium.

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: Pretreatment up to 22.5 hr; in vitro 5 sec to 30 min.

EXAM. TYPE: Biochemical

3527

COMPOUND: Phenethylamine, alpha-methyl-sulphate (2:1),(+,-)-

000060139

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 2 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Phenethylamine, alpha-methyl-, sulphate (2:1), (+-)-

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced increased locomotion, abnormal postures and arousal EEGs. Atropine sulfate and atropine methylnitrate potentiated the effects of this compound. Chlorpromazine HCl, reserpine phosphate, diphenhydramine HCl, cyclizine, chlorpheniramine maleate, promethazine HCl, meprobamate, phenoxybenzamine HCl blocked the effects of this compound.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-50 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Phenethylamine, 3,4,5,-trimethoxy-
000054046

REFERENCE: Dill, R.E. and Campbell, K.M.
Res. Comm. Chem. Path. Pharm. 6: 975-982, 1973.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced tremors in the contralateral limbs lasting 1/2-hour.

ANIMALS: Squirrel monkeys
Rats (details ns)

PREPARATION AND DOSE or HISTORY OF PATIENT: 161 or 540 nMoles/monkey
About 200-800 nMoles/rat

ROUTE AND SITE: Monkeys: direct application to putamen
Rats: intrastriatal

CONTROL INFORMATION: Homovanillic acid or saline

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical (behavior)

383

COMPOUND: Phenethylamine, 3,4,5,-trimethoxy-
000054046

REFERENCE: Seiler, N. and Demisch, L.
Biochem. Pharmacol. 23:273-287, 1974.

OBSERVED NEUROTOXIC EFFECTS: Probable formation of trimethoxyphenylacetic acids in the brain.

ANIMALS: Mice, NMRI, M, 30-35 g (groups of 10)

PREPARATION AND DOSE or HISTORY OF PATIENT: Various labeled compounds including 2,6-mescaline HCl 120 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: 1-24 hr. serial

EXAM. TYPE: Biochemical

384

COMPOUND: Phenethylamine, 3,4,5,-trimethoxy-
000054046

REFERENCE: Shah, M.S. and Neely, A.E.
Biochem. Pharmacol. 22:1535-1538, 1973.

OBSERVED NEUROTOXIC EFFECTS: Nontoxic doses of chlorpromazine caused "marked and prolonged retention" of compound blocking its disappearance from brain of both mother and fetuses.

ANIMALS: Mouse, Swiss-Webster, pregnant F (number ns.)

PREPARATION AND DOSE or HISTORY OF PATIENT: Labeled mescaline 8.33 micromoles/kg. Chlorpromazine up to 15 mg/kg, serially. Various schedules. Days 15-18 of gestation.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Incorporated into schedules

DURATION OF EXPERIMENT: 4 hr after mescaline, sacrifice

EXAM. TYPE: Biochemical

COMPOUND: Phenethylamine, 3,4,5-trimethoxy-, hemisulfate

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced excitement, abnormal postures, arousal EEGs, then depression.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-100 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Phenol

000108952

REFERENCE: Berry, K. and Olszewski, J.
Neurology 13: 152-154, 1963.

OBSERVED NEUROTOXIC EFFECTS: The treatment gave scant relief of pain, but caused severe demyelination, especially in the outer zone of the posterior roots, affecting fibers of all sizes.

ANIMALS: Human: 3 terminal cancer patients with intractable pain.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5-0.6 ml of 5% compound

ROUTE AND SITE: Intrathecal

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 12 d to 10-1/2 wk

EXAM. TYPE: Clinical, autopsy (histology)

385

COMPOUND: Phenol, p-(2-aminoethyl)-3-methoxy-

REFERENCE: Dill, R.E. and Campbell, K.M.
Res. Comm. Chem. Path. Pharm. 6: 975-982, 1973.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced tremors in the contralateral limbs lasting 1/2-hour.

ANIMALS: Squirrel monkeys
Rats (details ns)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 161 or 540 nMoles/monkey
About 200-800 nMoles/rat

ROUTE AND SITE: Monkeys: direct application to putamen
Rats: intrastriatal

CONTROL INFORMATION: Homovanillic acid or saline

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical (behavior)

386

COMPOUND: Phenol, m-(N-(2-imidazolin-2-ylmethyl)-p-toluidino)-, monoethanesulfonate (salt)
000065281

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 46 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Alder, S. and Zbinden, G.
Agents and Actions 3/4: 233-243, 1973.

OBSERVED NEUROTOXIC EFFECTS: Spongiform encephalopathy of brain and cord after 5 doses (10 and 15mg levels), severe after 9 doses; occasional degeneration of sciatic nerve. Mild atrophy of pancreas at 5 mg level. Hind leg paresis at 10 and 15mg levels. Slight delay on Hot Plate Test, no effects on Foot Print Test, failures of Rotating Rod Test after 4 (15mg level) and 10 (10mg level) days.

ANIMALS: Rats: CFN Zu, F, 38-53g, 8 groups 10-12 each

PREPARATION AND DOSE or HISTORY OF PATIENT: 5, 10, 15 mg/kg, 5 d/wk, 2 groups/level, 5-50 doses

ROUTE AND SITE: Oral

CONTROL INFORMATION: 2 groups water orally

DURATION OF EXPERIMENT: Serial sacr 1-10 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro) (Hexachlorophene)

000070304

REFERENCE: DeJesus, P.V., Jr. and Pleasure, D.E. Arch. Neurol. 29:180-182, 1973.

OBSERVED NEUROTOXIC EFFECTS: Low-Hexachlorophene rats few signs but motor nerve conduction velocity (MNCV) diminished, and yield of myelin sulfatide was low. High-Hexachlorophene rats had hind limb weakness and muscle-wasting (recovered in 1-2 wk), MNCV 72% diminished, and still lower yield of myelin sulfatide.

ANIMALS: Rats, Osborne-Mendel, adult, 3 grps

PREPARATION AND DOSE or HISTORY OF PATIENT: Low-Hexachlorophene fed diet giving 25-35 mg/kg/d. High-Hexachlorophene diet gave 50-75 mg/kg/d. Sciatic nerves extracted, on termination.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated group.

DURATION OF EXPERIMENT: About 2 mo.

EXAM. TYPE: Behavior; nerve-conduction; biochemistry

387

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Hall, G.A. and Reid, I.M. J. Path. 114:241-246, 1974.

OBSERVED NEUROTOXIC EFFECTS: Incoordination, varied extent(none to fatal). White-matter vacuolation in Central and Peripheral Nervous System, rapid onset, severe in some clinically normal animals.

ANIMALS: Sheep, Herdwick or (Suffolk x Clun Forest), F and castrated M yearlings, 3 studies with 9, 6, and 11 sheep.

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mg/kg/d as 5% w/v in paraffin.

ROUTE AND SITE: Oral (1,2); injection into rumen (3).

CONTROL INFORMATION: Paraffin only

DURATION OF EXPERIMENT: Serial sacr to 12 d

EXAM. TYPE: Behavior, histology

386 A

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro,-(hexachlorophene)

000070304

REFERENCE: Herter, W.B.
Kaiser Fdn. Hosp. Bull. 7:59, 1959.

OBSERVED NEUROTOXIC EFFECTS: Twitching, nystagmus, convulsions; recovery started on d 4 of hospital stay. On d 6, left facial paralysis; recovered by d 16. Author stated that no similar case of hexachlorophene poisoning was found in published reports.

ANIMALS: Human: baby, 5 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: 3% lotion applied and left there daily for 5 d.

ROUTE AND SITE: Topical, after bath, all over skin.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 11 d

EXAM. TYPE: Clinical

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Kimbrough, R.D. and Gaines, T.B.
Arch. Env. Hlth. 23:114-118, 1971.

OBSERVED NEUROTOXIC EFFECTS: Leg weakness at 2 wk, paralysis at 3-5 wk, recovery in 6 wk. Brain wt increased and returned to normal. Cerebral white-matter edema, diffuse spongy degeneration.

ANIMALS: Rats, Sherman, adult F

PREPARATION AND DOSE or HISTORY OF PATIENT: 500 ppm in diet (25 mg/kg/d)

ROUTE AND SITE: Oral

CONTROL INFORMATION: Matched untreated controls

DURATION OF EXPERIMENT: Serial sacr to 14 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Lampert, P., O'Brien, J. and Garrett, R.
Acta Neuropath. 23:326-333, 1973.

OBSERVED NEUROTOXIC EFFECTS: Lethargy, dragging hindlegs after 2 wk. Gross cerebral edema, especially white-matter (corpus callosum). Widely-spaced myelinated axons. Wide clear spaces within myelin sheaths (between lamellae). Spaces disappeared on recovery. Water content of brain had been increased, as had proportion of ganglioside GM_3. Little axonal degeneration.

ANIMALS: 10 Rats (Sherman) and 40 mice

PREPARATION AND DOSE or HISTORY OF PATIENT: 700-1000 ppm respectively in diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: 20 mice transferred to normal diet after 2 wk and so fed for up to 12 wk. Some normal-diet controls.

DURATION OF EXPERIMENT: 14 wk

EXAM. TYPE: Behavior, histology, biochemistry

389

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Martinez, A.J., Boehm, R. and Hadfield, M.G.
Acta Neuropath. 28:93-103, 1974.

OBSERVED NEUROTOXIC EFFECTS: Anorexia, nausea, vomiting; blurred vision, blindness; later somnolence, disorientation. Decerebrate posturing, respiratory and cardiac arrest. EEG slowed at 40 hr after admission, isoelectric at 71 hr. Demyelination and axonal degeneration throughout optic pathways, considered secondary to edema. Optic tract localization shown dependent on oral route, as in animal models.

ANIMALS: 1 Human: M, aged 7 yr

PREPARATION AND DOSE or HISTORY OF PATIENT: Accidental administration of 6 doses totaling approx. 45 ml 67-21 hr before admission to hospital.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Death 83 hr after admission

EXAM. TYPE: Behavior; Histology

390

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-
(Hexachlorophene)
000070304

REFERENCE: Matthieu, J-M., Zimmerman, A.W., Webster, H.deF., Ulsamer, A.G., Brady, R.O. and Quarles, R.H.
Exp. Neurol. 45:558-575, 1974.

OBSERVED NEUROTOXIC EFFECTS: 500 ppm fed d 1-10 had proved lethal. Now, lethargy, incontinence of urine, and spastic paraplegia in pups and dams, but pups placed on control diet at d 18 recovered in 4 wk. Central Nervous System white-matter was demyelinated, apparently following degradation of a myelin glycoprotein.

ANIMALS: Rats, S-D, 16 litters (9-10/litter) aged 2 d, randomized.

PREPARATION AND DOSE or HISTORY OF PATIENT: 300 ppm in SPF diet (15 mg/kg/d) days 2-10, then 500 ppm (25 mg/kg/d) days 11-18, fed to dams; same fed to pups days 19-21. On d 21 pups were injected intracerebrally with labeled fucose and sacrificed 16 hr later (d 22).

ROUTE AND SITE: Oral

CONTROL INFORMATION: Fed SPF diet without hexachlorophene.

DURATION OF EXPERIMENT: 22 d

EXAM. TYPE: Histology and biochemistry; behavior.

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: MaKaue, H.S., Dost, F.N. and Buhler, D.R.
Tox. Appl. Pharm. 24:239-249, 1973.

OBSERVED NEUROTOXIC EFFECTS: Lethargy, posterior paralysis, histopathological change in the brain, characterized by extensive vacuolization and edema of myelinated areas. Hind limb weakness, brain lesions and death.

ANIMALS: Rats, albino, Wistar, M and F, 4 wk old.

PREPARATION AND DOSE or HISTORY OF PATIENT: I.P.: 21.8-39.9 mg/kg/d.
Oral: 63.0-87.0 mg/kg/d.

ROUTE AND SITE: I.P. and oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Sacr 16 weeks, others demised.

EXAM. TYPE: Histology, hematology.

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Pilapil, V.R.
Am. J. Dis. Child. 11:333-336, 1966.

OBSERVED NEUROTOXIC EFFECTS: Neuromuscular signs by d 3-4, progressing to seizures. After correction of error, spastic flexion of extremities persisted at 1 wk, slight at 1 mo. (EEG normal at 2 wk, no observed residual signs at 6 mo.

ANIMALS: Human: one case, neonate, M

PREPARATION AND DOSE
or HISTORY OF PATIENT: 3% prep, 20 drops 4/d for 2 d, 25 drops 4/d, for 5 d, by mistake for sulfisoxazole (misbottling).

ROUTE AND SITE: Oral, gavage

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 7 d plus 6 mo. follow-up

EXAM. TYPE: Clinical

391

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-
(Hexachlorophene)

000070340

REFERENCE: Pleasure, D., Towfighi, J., Silberberg, D. and Parris, J.
Neurology 24:1068-1075, 1974.

OBSERVED NEUROTOXIC EFFECTS: (1) In vivo: hindlimb weakness in 2-3 wk, sciatic nerve demyelination, loss of about 40% of myelin.
(2) In vitro (rat brain): disruption of myelin within 12 hr.
(3) Chick embryo sciatic nerves: hexachlorophene was bound rapidly, inhibited protein and lipid synthesis after 1 hr and depleted the nerves of ATP.

ANIMALS: (1) Rats, Osborne-Mendel, adult, 30 including controls.
(2) Cultures of newborn rat cerebellum, 47 including control cultures.
(3) Sciatic nerves from chick embryos, 18 d old.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 0.1% in diet (w/w).
(2) Selected cultures exposed to 0.3-10 mcg/ml of medium for 48 hr on d 14-19 in vitro.
(3) Incubated for 2 hr with labeled myelin precursors and "sufficient" HCP, or with labeled HCP.

ROUTE AND SITE: (1) oral (2 and 3) in medium in vitro.

CONTROL INFORMATION: Controls as above without hexachlorophene.

DURATION OF EXPERIMENT: (1) up to 4 wk, (2) 48 hr (3) 2 hr.

EXAM. TYPE: Behavior, biochemistry, histology

392

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-
(Hexachlorophene)
000070304

REFERENCE: Rose, A.L., Wisniewski, H.M., and Cammer, W.
J. Neurol. Sci. 24:425-435, 1975.

OBSERVED NEUROTOXIC EFFECTS: Paralysis of hindlimbs. Survivor's vision was impaired. Myelin was vacuolated in central and peripheral nervous system with axonal degeneration, especially in optic nerves. After treatment stopped, poisoned infants had hydrocephalus, optic nerve atrophy. 50% of dams and 75% infants died. Hexachlorophene in blood: dams 4.7-6 mcg/ml, infants 2-2.5 mcg/ml.

ANIMALS: 23 Rats, S-D, F with nursing litters (20 were ttd).

PREPARATION AND DOSE
or HISTORY OF PATIENT: 500 ppm in dams' diet (50 mg/kg/d) from 9th d postpartum. Young received same diet from weaning.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 3 dams and litters untreated, diet alone.

DURATION OF EXPERIMENT: Serial sacr to 180 d.

EXAM. TYPE: Behavior, biochemistry, histology

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-
(Hexachlorophene)
000070304

REFERENCE: Shuman, R.M., Leech, R.W., and Alvord, E.C.
Arch. Neurol. 32: 315-319, 1975.

OBSERVED NEUROTOXIC EFFECTS: Inactivity decreased feeding, weakness, coarse tremor; "extremely susceptible" at age 6-22 d, not susceptible after d 26, or before d 2. Vacuolar encephalopathy was produced by 2 washes only between d 13 and 22. Vacuolization and disruption of myelin, no damage to nonmyelinated nuclear areas. "Age-dose-response curves are similar to those in humans."

ANIMALS: Rats aged 0-33 d kept with dams

PREPARATION AND DOSE
or HISTORY OF PATIENT: Daily wash with 3% hexachlorophene in detergent, 2-3 ml.

ROUTE AND SITE: Topical

CONTROL INFORMATION: 2 litters washed with detergent only, one litter unwashed.

DURATION OF EXPERIMENT: 33 d, serial termination.

EXAM. TYPE: Behavior, histology

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-(Hexachlorophene)

000070304

REFERENCE: Shuman, R.M., Leech, R.W. and Alvord, E.C. Arch. Neurol. 32: 320-325, 1975.

OBSERVED NEUROTOXIC EFFECTS: Whole-body bathing repeatedly in 3% hexachlorophene (history) significantly associated with vacuolar encephalopathy of brainstem reticular formation; prevalence related to number of exposures, concentration of hexachlorophene, thoroughness of rinsing, and exposure to UV.

ANIMALS: Human neonates under 1.4 kg birthweight that survived 4 or more d and were autopsied from 1/1/66 through 6/30/73; total of 46, in 2 hospitals.

PREPARATION AND DOSE or HISTORY OF PATIENT: Available brain sections, with 2 or more brainstem levels (medulla and either pons or midbrain). Histories examined independently and then matched with histology data.

ROUTE AND SITE: Topical (washing)

CONTROL INFORMATION: Blind review of 2 sets of data.

DURATION OF EXPERIMENT: 18 mo.

EXAM. TYPE: Histology and history

393>

COMPOUND: Phenol, 2.2'-methylenebis (3.4.6-trichloro)-

000070304

REFERENCE: Stenbäck, F. Arch. Env. Hlth. 30:32-35, 1975.

OBSERVED NEUROTOXIC EFFECTS: Hindlimb tremor, paralysis, convulsions, death (22% in 2 wk, thereafter mortality unremarkable). Symptoms vanished after 2-6 wk, epidermis at site thickened. Autopsies showed edema and cystic lesions in Central Nervous System white-matter; some of the lesions persisted after symptoms had vanished.

ANIMALS: Mice, random-bred Swiss, F, age 8 wk.

PREPARATION AND DOSE or HISTORY OF PATIENT: 5, 25 or 50% in 0.2 ml acetone, 2 doses/wk for life, 50 mice/conc.

ROUTE AND SITE: Topical, dorsal skin between flanks, shaved regularly

CONTROL INFORMATION: One control group.

DURATION OF EXPERIMENT: Lifetime

EXAM. TYPE: Behavior, clinical, autopsy, histology

394

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Udall, V.
Proc. Roy. Soc. Med. 65: 197-199, 1972

OBSERVED NEUROTOXIC EFFECTS: Signs 12-30 hours after dose included loss of visual acuity and pupil response (no recovery after 4 mo), transient optic disc edema, no retino-EEG action potentials, exophthalmos, cerebral edema.

ANIMALS: Sheep and Cattle

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20-80 mg/kg

ROUTE AND SITE: Oral, abomasal, or ruminal

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, physiology

COMPOUND: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-

000070304

REFERENCE: Webster, Henry DeF., Ulsamer, A.G. and O'Connell, M.F.
J. Neuropath. Exp. Neurol. 33(1):144-170, 1970.

OBSERVED NEUROTOXIC EFFECTS: Large optical lesions, myelin sheath splitting at axonal and extracellular surfaces, vacuolation in myelin sheaths, ventral tail nerve fibers exhibited focal splitting and lesions on peripheral myelin sheath. Loss of some motor activity.

ANIMALS: 25-40 groups Tadpoles, Xenopus, 45-55th development stage.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Immersed in 0.1-0.2 mcg Compound/ml.

ROUTE AND SITE: Absorption via immersion

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Sacr 1, 3, 5, 6 or 7 d.

EXAM. TYPE: Ultrastructural, histology

COMPOUND: Phenolphthalein

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115:199-205, 1975

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus in colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m.

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

395

COMPOUND: Phenothiazine drugs (unspecified)

REFERENCE: Myrianthopoulos, N.C., Kurland, A.A. and Kurland, L.T.
Arch. Neurol. 6: 19-23, 1962.

OBSERVED NEUROTOXIC EFFECTS: 13 cases of parkinsonism found among relatives of propositi, 3 among relatives of controls; numbers too small for analysis but suggested some hereditary susceptibility to parkinsonian side-effects of ataractic drugs.

ANIMALS: Human: 728 relatives of 59 propositi

PREPARATION AND DOSE or HISTORY OF PATIENT: History of high doses of compounds with parkinsonian side-effects

ROUTE AND SITE: Oral

CONTROL INFORMATION: 777 relatives of 67 controls

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Epidemiology

396

COMPOUND: Phenothiazine, 2-chloro-10-3(3-dimethylamino)propyl)- (chloropromazine)
000050533

REFERENCE: Brosnan, C.F., Bunge, M.B. and Murray, M.R.
J. Neuopath. Exp. Neurol. 24(3):337-353, 1970.

OBSERVED NEUROTOXIC EFFECTS: Chlorpromazine affected the lysosomal system, inducing acid Pase activity; compound appeared to be concentrated within the multilaminated dense bodies of the lysosomal system. The purpose of the study was to explore the mode of action of chloropromazine.

ANIMALS: Rat ganglia from 18-19 d fetuses, cultured in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.0×10^{-5} M or 1.4×10^{-4} M in salt solution, 74 cultures examined.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Controls with substrate alone, or no substrate.

DURATION OF EXPERIMENT: Weeks

EXAM. TYPE: Cytology, biochemistry

COMPOUND: Phenothiazine, 2-chloro-10-3(3-dimethylamino)propyl)-
000050533

REFERENCE: Shah, N.S. and Neely, A.E.
Biochem. Pharmacol. 22:1535-1538, 1973.

OBSERVED NEUROTOXIC EFFECTS: Nontoxic doses of chlorpromazine caused "marked and prolonged retention" of mescaline, blocking its disappearance from brain of both mother and fetuses.

ANIMALS: Mouse, Swiss-Webster, pregnant F (number ns.)

PREPARATION AND DOSE or HISTORY OF PATIENT: Labeled mescaline 8.33 micromoles/kg. Chlorpromazine up to 15 mg/kg, serially. Various schedules. Days 15-18 of gestation.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Incorporated into schedules

DURATION OF EXPERIMENT: 4 hr after mescaline, sacrifice

EXAM. TYPE: Biochemical

COMPOUND: Phenothiazine, 2-chloro-10-3(3-dimethylamino)propyl)-

000050533

REFERENCE: Sturman, G.
Br. J. Pharmac. 50: 153-155, 1974.

OBSERVED NEUROTOXIC EFFECTS: Mice: Pretreatment 1 hour beforehand with piperazine enhanced the acute toxicity of chlorpromazine but not of prochlorperazine. Rats: Pretreatment with piperazine enhanced catatonia from chlorpromazine but not from prochlorperazine. Piperazine did not alter the EEG changes induced by chlorpromazine or prochlorperazine. In sum: piperazine potentiated the central nervous system effects of chlorpromazine but not of prochlorperazine.

ANIMALS: Mice, no details
Rats, F, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: Piperazine: 0, 1, 2.5 or 5 g/kg^{-1} followed after 1 or 24 hr by various doses of chlorpromazine or prochlorperazine

ROUTE AND SITE: Piperazine: S.C.; chlorpromazine and prochlorperazine: I.P.

CONTROL INFORMATION: No piperazine given

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Behavior

397<

COMPOUND: Phenothiazine, 2-chloro-10-(3-(dimethylamino)propyl)-,mono-hydrochloride

000069090

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 7 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

398

COMPOUND: Phenothiazine, 2-chloro-10-(3-(dimethylamino)propyl)-, mono-hydrochloride

000069090

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966.

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 2.5-50 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Phenothiazine, 2-chloro-10-(3-(4-methyl-1-piperazinyl) propyl

000058388

REFERENCE: DeSilva, K.L., Muller, P.J. and Pearce, J.
Practitioner 211: 316-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Extrapyramidal signs, spasms especially of face, tongue and jaws, torticollis, opisthotonus, trismus; onset in 2-60 hrs. commonest in young. No dose relationship, recovery after withdrawal. One case had added diencephalic features. Authors comment that etiology still unknown, and suggest idiosyncracy to class of drugs (phenothiazines).

ANIMALS: Human: 10 cases, M & F, 14-30, selected from 20 cases treated at a hospital serving 500,000 population, over 2 yrs

PREPARATION AND DOSE or HISTORY OF PATIENT: 3 cases: 15 mg P.O., 12.5 to 25 mg I.M. Adverse drug reaction.

ROUTE AND SITE: I.M. and P.O. (see above)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 2-24 hrs.

EXAM. TYPE: Clinical

COMPOUND: Phenothiazine, 2-chloro-10-(3-(4-methyl-1-piperazinyl)propyl- (prochlorperazine)

000058388

REFERENCE: Sturman, G.
Br. J. Pharmac. 50: 153-155, 1974.

OBSERVED NEUROTOXIC EFFECTS: Mice: Pretreatment 1 hour beforehand with piperazine enhanced the acute toxicity of chlorpromazine but not of prochlorperazine. Rats: Pretreatment with piperazine enhanced catatonia from chlorpromazine but not from prochlorperazine. Piperazine did not alter the EEG changes induced by chlorpromazine or prochlorperazine. In sum: piperazine potentiated the central nervous system effects of chlorpromazine but not of prochlorperazine.

ANIMALS: Mice, no details
Rats, F, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: Piperazine: 0, 1, 2.5 or 5 g/kg^{-1} followed after 1 or 24 hr by various doses of chlorpromazine or prochlorperazine

ROUTE AND SITE: Piperazine: S.C.; chlorpromazine and prochlorperazine: I.P.

CONTROL INFORMATION: No piperazine given

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Behavior

339

COMPOUND: Phenothiazine, 10-(2-diethylamino) propyl)-

000522009

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

400>

COMPOUND: Phenothiazine, 10-(2-dimethylamino propyl)

000060877

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 16 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Phenothiazine, 10-(3-(dimethylamino)propyl)-, monohydrochloride (promazine)

000053601

REFERENCE: Baron, J.A. and Kline, N.S.
Am. J. Psychiatry 113: 654, 1957.

OBSERVED NEUROTOXIC EFFECTS: "A few" developed mild rigidity; 2 patients had grand mal seizures. When the dose was reduced to 200 mg four times per day, there were no adverse reactions. An EEG taken in 1 case was normal.

ANIMALS: Human: schizophrenics, subjects of a clinical pharmacology trial, ages 25-68, hospitalized 2-24 yr, total 21 subjects

PREPARATION AND DOSE or HISTORY OF PATIENT: All had been receiving chlorpromazine for 6 mo or more. Promazine given 25-300 mg four times per day.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 3 mo or more

EXAM. TYPE: Clinical

COMPOUND: Phenothiazine, 10-(3-(dimethylamino)propyl)-, monohydrochloride

000053601

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 9 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

401

COMPOUND: Phenothiazine, 10-(2-(dimethylamino) propyl)-, monohydrochloride

000058333

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >50 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

402

COMPOUND: Phenothiazine, 2-(ethylthio)-10-(3-(4-methyl-1-piperazinyl)propyl)-

REFERENCE: DeSilva, K.L., Muller, P.J. and Pearce, J.
Practitioner 211: 316-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Extrapyramidal signs, spasms especially of face, tongue and jaws, torticollis, opisthotonus, trismus; onset in 2-60 hrs. commonest in young. No dose relationship, recovery after withdrawal. One case had added dienceph-alic features. Authors comment that etiology still unknown, and suggest idiosyncracy to class of drugs (phenothiazines).

ANIMALS: Human: 10 cases, M & F, 14-30, selected from 20 cases treated at a hospital serving 500,000 population, over 2 yrs

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 case: 10 mg, t.d.s., P.O.
Adverse drug reaction.

ROUTE AND SITE: T.d.s., P.O. (see above)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 60 hrs.

EXAM. TYPE: Clinical

COMPOUND: Phenothiazine, 10-(3-(4-methyl-1-piperazinyl)propyl)-2-(trifluoromethyl)-

REFERENCE: DeSilva, K.L., Muller, P.J. and Pearce, J.
Practitioner 211: 316-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Extrapyramidal signs, spasms especially of face, tongue and jaws, torticollis, opisthotonus, trismus; onset in 2-60 hrs. commonest in young. No dose relationship, recovery after withdrawal. One case had added dienceph-alic features. Authors comment that etiology still unknown, and suggest idiosyncracy to class of drugs (phenothiazines).

ANIMALS: Human: 10 cases, M & F, 14-30, selected from 20 cases treated at a hospital serving 500,000 population, over 2 yrs

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 case: 1 mg, b.d., P.O.
Adverse drug reaction.

ROUTE AND SITE: B.d., P.O. (see above)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 60 hrs.

EXAM. TYPE: Clinical

COMPOUND: Phenothiazine, 10-(3-(4-methyl-1-piperazinyl)propyl)-2-trifluoromethyl)-

REFERENCE: Romasenko, V.A. and Jacobson, I.S.
Acta Neuropath. 12:23-32, 1969.

OBSERVED NEUROTOXIC EFFECTS: "Sluggishness, motor inhibition, and catalepsy" reversed on stopping the drug. Vascular changes and hyperchromic and "wrinkled" nerve cells in cerebral cortex. Increased RNA, proteins, SH-groups, and polysaccharides. Diminished activities of acid phosphatase and succinic dehydrogenase. Some Purkinje cells affected in cerebellum. Author concluded changes are very slight and reversible.

ANIMALS: 96 Rats, white, M, 150-250 g

PREPARATION AND DOSE or HISTORY OF PATIENT:
1. Chronic: 1, 5, or 20-25 mg/kg for 1-5 wk.
2. Acute and subacute: 50-250 mg/kg, one dose.
3. Observational only.

ROUTE AND SITE: 1. Oral: gavage or in diet. 2. I.M.

CONTROL INFORMATION: Mentioned, not described.

DURATION OF EXPERIMENT: 1. about 2 mo. 2. 30 min. 3. 1 mo. after (1)

EXAM. TYPE: Behavior, biochemistry, histology

403

COMPOUND: 3-Phosphabicyclo(4.4.0) decane, p-chloro-2,4-dioxa-3-methyl-p-thioxo-

REFERENCE: Sherman, H., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.
Acute: Significant growth depression even at levels lower than the LD_{50}.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) Acute: LD_{50} 25.6 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

404

COMPOUND: Phosphine oxide, tri-o-tolyl-

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G. Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: None had paralysis.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg.
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphofluoridic acid, methyl-, isopropyl ester

000107448

REFERENCE: Bajgar, J.
Tox. and App. Pharm. 22:93-96, 1972.

OBSERVED NEUROTOXIC EFFECTS: Acetylcholinesterase inhibition in blood and subcellular fractions of medulla oblong gata.

ANIMALS: Rats, Wistar/Mazno, F, 150-170 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.2 mg/kg (approximating LD_{50}).

ROUTE AND SITE: I.M.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Immediately

EXAM. TYPE: Histological, biochemical

COMPOUND: Phospholipase A

REFERENCE: Chang, C.C., Chuang, S-T., Lee, C.Y., Wei, J.W.
Br. J. Pharmac. 44:752-764, 1972.

OBSERVED NEUROTOXIC EFFECTS: Ineffective on axonal conduction. Synergistic effect on cardiotoxin's blocking action due to aceleration rather than potentiation of its action. 90 mcg/ml completely depolarized superficial muscle fibers. High concentrations of $CaCl_2$ enhanced the depolarizing effect.

ANIMALS: Phrenic nerve-diaphragm preparation from Long-Evans rats.

PREPARATION AND DOSE or HISTORY OF PATIENT: Various doses in vitro.

ROUTE AND SITE: In vitro.

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Electrophysiology, chemistry.

405

COMPOUND: Phosphonic acid, decyl-, ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

406

COMPOUND: Phosphonic acid, ethyl-, 2-chloroethyl 2,2-dichlorovinyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphonic acid, O-ethyl-O-(4-nitrophenyl)-ethyl ester

REFERENCE: Rosic, N., Lonax, P. and Kovacevic, N.
Comp. Gen. Pharm. 5: 187-189, 1974.

OBSERVED NEUROTOXIC EFFECTS: Avoidance behavior was depressed up to 6 hr after treatment with recovery by 24 hr. Brain cholinesterase was down 20% by 2 hr, returning after 6 hr, and recovered by 24 hr. The authors suggest these findings are related.

ANIMALS: Fish (Serranus scriba), 15-25 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 60 mcg/kg after avoidance training (half LD_{50})

ROUTE AND SITE: S. C.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Serial to 24 hr

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Phosphonic acid, pentyl-, ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

407<

COMPOUND: Phosphonic acid, 2-phenylethyl-, ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

408

COMPOUND: Phosphonic acid, phenylmethyl-, ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15: 541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology.

COMPOUND: Phosphonic acid, 3-phenylpropyl-, ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphonic acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester

000052686

REFERENCE: Rayner, M.D., Popper, J.S., Carvalho, E.W. and Hurov, R.
Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE: Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

409

COMPOUND: Phosphonodithioic acid, chloromethyl-, S-(p-chlorophenyl)O-isopropyl ester

001713979

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 30.9 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

410

COMPOUND: Phosphonodithiotic acid, O-isopropyl-S-p-tolyl chloromethyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 34.1 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphonofluoridic acid, methyl-, isopropyl ester

REFERENCE: Loomis, T.A.
Tox. Appl. Pharm. 5:489-499, 1963.

OBSERVED NEUROTOXIC EFFECTS: Motor activity in activity-cage decreased.

ANIMALS: Mice, white, 25-30 g, and 2 dogs (no details)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mcg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline treated controls.

DURATION OF EXPERIMENT: Serial sacr to 25 min.

EXAM. TYPE: Biochemistry, behavior

COMPOUND: Phosphonofluoridic acid, methyl-, isopropyl ester

REFERENCE: Loomis, T.A. and Salafsky, B.
Tox. Appl. Pharm. 5:685-701, 1963.

OBSERVED NEUROTOXIC EFFECTS: Acetylcholinesterase inhibition.

ANIMALS: Mice, C_3H, 25-35 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.01 ml

ROUTE AND SITE: Dermal

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Mortality, electrophysiology

411>

COMPOUND: Phosphonofluoridic acid, methyl-, 1,2,2-trimethylpropyl ester

000096640

REFERENCE: Loomis, T.A. and Salafsky, B.
Tox. Appl. Pharm. 5:685-701, 1963.

OBSERVED NEUROTOXIC EFFECTS: Acetylcholinesterase inhibition

ANIMALS: Mice, C_3H, 25-35 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.01 ml

ROUTE AND SITE: Dermal

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Mortality, electrophysiology

412

COMPOUND: Phosphonothioic acid, ethyl-, di(2-chloroethyl) ester.

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphonothioic acid, ethyl-, O-ethyl O-(2,4,5-trichlorophenyl) ester

000327980

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS of esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology.

COMPOUND: Phosphonothioic acid, ethyl-, O-ethyl O-(2,4,5-trichlorophenyl) ester

000327980

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 12.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

413<

COMPOUND: Phosphonothioic acid, methyl-, 2,4-dichlorphenyl methyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

414

COMPOUND: Phosphonothioic acid, phenyl,-O-ethyl ester, O-ester with p-hydroxybenzonitrile

013067931

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 20.3 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphonothioic acid, phenyl-,O-ethyl O- (p-nitrophenyl)ester

002104645

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 80 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphonothioic acid, O-ethyl S-(2-dimethyl amino ethyl methyl ester

REFERENCE: Bajgar, J.
Br. J. Pharmac. 45: 368-371, 1972.

OBSERVED NEUROTOXIC EFFECTS: Acetylcholinesterase inhibition in 3 parts of the medulla oblongata proceeded at different rates. The author concluded that penetration of the compound through corresponding parts of the blood-brain barrier was not uniform.

ANIMALS: Rats, Wistar, F, 150-170 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.035 mg/kg

ROUTE AND SITE: I.M.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1-30 min

EXAM. TYPE: Biochemistry

415<

COMPOUND: Phosphonotrithioic acid, S,S-dipropyl methyl

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 11.6 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

416

COMPOUND: Phosphonotrithioic acid, methyl-, S-propyl-S-diethylsuccinate

REFERENCE: Sherman, H., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 96.1 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphoramidic acid, methyl-, 4-tert-butyl-2-chlorophenyl methyl ester

000299865

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 400 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphoramidic acid, methyl-4-tert-butyl-2-chlorophenyl methyl-ester

000299865

REFERENCE: Khan, M.A.
Res. Vet. Sci. 15: 180-185, 1973.

OBSERVED NEUROTOXIC EFFECTS: The animals exhibited dullness, ataxia and muscular fasciculation, with recovery in 72 hr (1 case 1 wk). The signs were related to inhibition of whole-blood cholinesterases.

ANIMALS: Calves, 5-7 mo, from herd with history of grub-infestation.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Sprayed with 0.5% aqueous solution of compound
(2) Pour-on application of 1:2 dilution of 25% compound
(3) Water only (control)

ROUTE AND SITE: Topical

CONTROL INFORMATION: Vehicle

DURATION OF EXPERIMENT: Serial to 8 wk

EXAM. TYPE: Biochemistry

417>

COMPOUND: Phosphoramidothioic acid, isopropyl-,O-2,4-dichlorophenyl O-methyl ester

000299854

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Lethargy and ataxia, followed by death over a 7-day period. (2) 50% cholinesterase inhibition by dose of 200 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} (1357.0 mg/kg) in gelatin capsule, 4-5 dose levels tested.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

418

COMPOUND: Phosphoric acid, aluminum salt

REFERENCE: Seil, F.J., Lampert, P.W. and Klatzo, I.
J. Neuropath. Exp. Neurol. 28: 74-85, 1969.

OBSERVED NEUROTOXIC EFFECTS: Induced neurofibrillary spheroids filled the cytoplasm of the cells exposed to aluminum phosphate, and the nuclei were displaced. The spheroids were compared with those induced by vincristine sulfate. The author claimed the former were like those of postencephalitic parkinsonism and the latter like those of Alzheimer's disease.

ANIMALS: In vitro cultures of spinal cord and dorsal root ganglia from fetal NZ White rabbits.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1:100 suspension every 4 d after 20-22 d in vitro: time of exposure 6-11 d in each cycle of 20 d

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Untreated cultures

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Light and electron microscopy

COMPOUND: Phosphoric acid, bis(2-ethylhexyl) o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis reported.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, bis(p-ethylphenyl) ester

REFERENCE: Boudy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W.
Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: (1) All birds were severely paralyzed.
(2) All birds developed ataxia within 12 days.
(3) All birds developed ataxia within 10 days.

ANIMALS: (1) 12 Chickens
(2) 3 Chickens
(3) 3 Chickens

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 1,000 mg/kg
(2) 500 mg/kg
(3) 100 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

419

COMPOUND: Phosphoric acid, bis(4-ethylphenyl) 2-propylphenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

420

COMPOUND: Phosphoric acid, bis(2-ethylphenyl) p-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

COMPOUND: Phosphoric acid, bis(o-propylphenyl) p-tolyl ester

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W.
Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: All birds developed ataxia within 10 days.

ANIMALS: 6 Chickens

PREPARATION AND DOSE
or HISTORY OF PATIENT: 500 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, bis (3,5-xylyl) 2-ethylphenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

421<

COMPOUND: Phosphoric acid, 2-chloro-1-(2,4-dibromophenyl) vinyl dimethyl ester

REFERENCE: Morallo, B.D. and Sherman, M.
J. Econ. Entomol. 60:509-515, 1967.

OBSERVED NEUROTOXIC EFFECTS: The order of resistance to the insecticide was: fleshfly > house fly > anthomyiid fly > blow fly. This insecticide caused 50% mortality in the anthomyiid fly within one hour, but was much slower with the other species. It caused a low level of inhibition of cholinesterase in house flies, but caused high levels in the other species, with maximum inhibition occurring within 30 minutes. Recovery was not very complete in anthomyiid flies and flesh flies.

ANIMALS: Housefly, Musca domestica, adult F, 3-4 d old
Anthomyiid fly, Fannia pusio, adult F, 3-4 d old
Blowfly, Chrysoma megacephala, adult F, 3-4 d old
Flesh fly, parasarcophaga argyrostoma, adult F, 3-4 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: In vitro: The LD_{50} (0.26-21.6 mcg/g), 10-20 flies/group or dose-level, each test replicated 3 or more times.
In vivo: 10 groups of 50 each of houseflies and anthomyiid flies, and 10 groups of 20 each of blowflies and flesh flies.

ROUTE AND SITE: Applied topically, venter of thorax.

CONTROL INFORMATION: Untreated fly heads

DURATION OF EXPERIMENT: Serial to 24 hr.

EXAM. TYPE: Biochemistry, mortality

COMPOUND: Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl ester

00047096

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 29.1 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl) vinyl dimethyl ester

002274371

REFERENCE: Morallo, B.D. and Sherman, M.
J. Econ. Entomol. 60:509-515, 1967.

OBSERVED NEUROTOXIC EFFECTS: The order of resistance to the insecticide was flesh fly >house fly >anthomyiid fly > blow fly. This insecticide is a relatively rapid toxicant, with 50% mortality occurring within one hour. 100% inhibition of cholinesterase occurred in the flesh fly within 5 minutes. Inhibition was higher and recovery less complete in dead flies than in living flies.

ANIMALS: Housefly, Musca domestica, adult F, 3-4 d old
Anthomyiid fly, Fannia pusio, adult F, 3-4 d old
Blowfly, Chrysoma megacephala, adult F, 3-4 d old
Flesh fly, parasarcophaga argyrostoma, adult F, 3-4 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: In vitro: The LD_{50} (0.26-21.6 mcg/g), 10-20 flies/group or dose-level, each test replicated 3 or more times.
In vivo: 10 groups of 50 each of houseflies and anthomyiid flies, and 10 groups of 20 each of blowflies and flesh flies.

ROUTE AND SITE: Applied topically, venter of thorax.

CONTROL INFORMATION: Untreated fly heads

DURATION OF EXPERIMENT: Serial to 24 hr.

EXAM. TYPE: Biochemistry, mortality

COMPOUND: Phosphoric acid, 2-chloro-1-(2,5-dichlorophenyl) vinyl dimethyl ester

REFERENCE: Morallo, B.D. and Sherman, M.
J. Econ. Entomol. 60:509-515, 1967.

OBSERVED NEUROTOXIC EFFECTS: The order of resistance to the insecticide was: flesh fly > house fly > anthomyiid fly > blow fly. This toxicant caused 50% mortality in all flies within 2 hours. Within 5 minutes, 90% inhibition of cholinesterase occurred in both house flies and flesh flies. Anthomyiid flies took 2 hours to reach maximum inhibition (49%). The recovery of the flesh fly was very slow with 50% inhibition after 24 hours.

ANIMALS: Housefly, Musca domestica, adult F, 3-4 d old
Anthomyiid fly, Fannia pusio, adult F, 3-4 d old
Blowfly, Chrysoma megacephala, adult F, 3-4 d old
Flesh fly, parasarcophaga argyrostoma, adult F, 3-4 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: The LD_{50} (0.26-21.6 mcg/g), 10-20 flies/group or dose-level, each test replicated 3 or more times.
In vivo: 10 groups of 50 each of houseflies and anthomyiid flies, and 10 groups of 20 each of blowflies and flesh flies.

ROUTE AND SITE: Applied topically, venter of thorax.

CONTROL INFORMATION: Untreated fly heads

DURATION OF EXPERIMENT: Serial to 24 hr.

EXAM. TYPE: Biochemistry, mortality

423

COMPOUND: Phosphoric acid, 2-chloroethyl 2,2-dichlorovinyl methyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

424

COMPOUND: Phosphoric acid, 2-chloroethyl 2-dichlorovinyl methyl ester

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions and death within 18 hrs. Survivors were lethargic for 6-19 hrs. post treatment.
(2) 50% Cholinesterase inhibited by doses of >800 ppm

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (37.8 mg/kg) as gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

COMPOUND: Phosphoric acid, 2-chloroethyl ethyl p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphoric acid, o-chlorophenyl diphenyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

4C25

COMPOUND: Phosphoric acid, 1-((p-chlorophenyl)thio) vinyl dimethyl ester

002595531

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 51.3 mg/kg
(2) Subacute: ^{50}50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

426

COMPOUND: Phosphoric acid, 2-chloro-1-(2,4,5-trichloro-phenyl)vinyl dimethyl ester

000961115

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 2528 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphoric acid, o-cresyl diphenyl ester

REFERENCE: Johnson, M.K. and Barnes, J.M.
Biochem. Pharm. 19:3045-3047, 1970.

OBSERVED NEUROTOXIC EFFECTS: Toxic to adult hens at 0.1 mg/kg. Repeated doses produced ataxia and "characteristic" lesions in cord and peripheral nerves.

ANIMALS: Chickens, various breeds, sex not stated.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 ml/kg, then 0.1 ml/kg up to 6 doses.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: Up to 63 d

EXAM. TYPE: Behavior, then histology. Also, in vitro bioassay.

COMPOUND: Phosphoric acid, cyclic methylene-o-phenylene o-tolyl ester

REFERENCE: Baron, R.L. and Casida, J.E.
Biochem. Pharm. 11: 1129-1136, 1962.

OBSERVED NEUROTOXIC EFFECTS: Ataxic doses inhibited selectively nerve esterases hydrolyzing butyryl esters of choline, glycerol and phenols. TOCP more persistent than metabolite. Oxidation of succinate, pyruvate, α-ketoglutarate by nerve and brain preparations was not affected.

ANIMALS: Chickens, White Leghorn, 1-2 y, 1.5-2.5 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20mg/kg

ROUTE AND SITE: TOCP: gavage; DFP and metabolite: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry

4274

COMPOUND: Phosphoric acid, cyclic methylene-o-phenylene tolyl ester

REFERENCE: Baron, R.L., Bennett, D.R. and Casida, J.E.
Br. J. Pharmacol. 18:465-474, 1962.

OBSERVED NEUROTOXIC EFFECTS: Clinical and neurological comparison was made between this compound and tri-ortho-cresyl phosphate. Ataxia was present with both, higher doses increased the degree of peripheral neuropathy. Demyelination of the spinal cord occurred at doses below those effecting peripheral nerve degeneration. Axon and myelin damage was prominent with both agents.

ANIMALS: 24 Chickens, White Leghorn, aged 12-18 mo, av 2 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 8-400 mg/kg in corn oil, single dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology

428

COMPOUND: Phosphoric acid, cyclic methylene-o-phenylene o-tolyl ester

REFERENCE: Taylor, J.D.
Tox. Appl. Pharmac. 11:538-545, 1967.

OBSERVED NEUROTOXIC EFFECTS: (1) Paralysis as from TOCP in 21 d. (2) Doses over 75 mg/kg to adults produced ataxia and an abnormal reflex; no effect on kittens. Axonal degeneration in cord, as from TOCP, found in cats.

ANIMALS: (1) One White Leghorn chicken
(2) 18 Cats, adult M, random-bred, castrated, and 8 kittens

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 10 mg/kg, one dose.
(2) 15-200 mg/kg, one dose.

ROUTE AND SITE:(1)ns. (2) I.M. in shoulder

CONTROL INFORMATION: (1) One control chicken
(2) 4 of the 8 kittens.

DURATION OF EXPERIMENT: Up to 190 d.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, 1,2-dibromo-2,2-dichloroethyl dimethyl ester
000300765

REFERENCE: Rayner, M.D., Popper, J.S., Carvalho, E.W. and Hurov, R.
Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE: Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

COMPOUND: Phosphoric acid, di(2-chloroethyl) 2,2-dichlorovinyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

429

COMPOUND: Phosphoric acid, di(2-chloroethyl) p-nitrophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4 RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

430

COMPOUND: Phosphoric acid, di(2-chloroethyl) 2,3,5-trichlorophenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphoric acid, di-o-chlorophenyl phenyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, 2-2-dichlorovinyl dimethyl ester

000062737

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

431

COMPOUND: Phosphoric acid, diethyl p-nitrophenyl ester

000311455

REFERENCE: Murphy, S.D., Lauwerys, R.R. and Cheever, K.L.
Tox. Appl. Pharm. 12: 22-35, 1968.

OBSERVED NEUROTOXIC EFFECTS: Inhibits brain cholinesterase.
Sensitivities: birds > mammals > fish.

ANIMALS: Mice, Swiss-Webster, M, 25-30g
Chickens, White Rock X N.H. Red, M, 500-700g
Sunfish, M and F, 40-80g
Bullfish, M and F, 40-80g
In vitro brains of rats, guinea pigs, sparrows, smallmouth bass, flounder, sculpin and monkey.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-1500 mg/kg, various schedules (I.P.) in mice, chickens, sunfish and bullheads; 0.1-200 mg/kg (orally) in sunfish; 0.001-4 picomoles of malaoxon in vitro.

ROUTE AND SITE: See above

CONTROL INFORMATION: Brain cholinesterase determined in controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry

COMPOUND: Phosphoric acid, di(o-ethylphenyl) p-tolyl ester

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W.
Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: Three out of four birds became paralyzed.

ANIMALS: 4 Chickens

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5 x 500 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, diethyl o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.C., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 0.5 gm/kg.
(2) 1.0 gm/kg.

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, dimethyl (1-(dimethylphosphonyl)vinyl) ester

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions and death within 18 hrs. Survivors were lethargic for 6-19 hrs. post treatment.
(2) 50% Cholinesterase inhibited by doses of 45 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (43.9 mg/kg) as gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

433

COMPOUND: Phosphoric acid, dimethyl ester, ester with (E)-3hydroxy-N-methyl crotonamide
000919448

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 3.54 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 3 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

4347

COMPOUND: Phosphoric acid, diphenyl o-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

COMPOUND: Phosphoric acid, diphenyl o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: All had paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg.
(2) 1.0 gm/kg.

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, di-o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice. E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.0 gm/kg
(2) 2.5 gm/kg in 5 aliquots over 10 d period.

ROUTE AND SITE: (1) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

435A

COMPOUND: Phosphoric acid, di-p-tolyl 2-ethylphenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

436-A

COMPOUND: Phosphoric acid, di-p-tolyl o-ethylphenyl ester

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W. Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: All chickens were paralyzed.

ANIMALS: (1) 5 Chickens
(2) 3 Chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Single dose of 1,000 mg/kg
(2) Single dose of 250 mg/kg
(3) Single dose of 50 mg/kg or 5 x 10 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, di-o-tolyl m-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M. Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

COMPOUND: Phosphoric acid, di-p-tolyl o-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

4372

COMPOUND: Phosphoric acid, di-o-tolyl p-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: Paralysis seen in all groups.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.4 gm/kg
(2) 0.2 gm/kg
(3) 0.1 gm/kg
(4) 0.05 gm/kg
(5) 0.025 gm/kg
(6) 2.5 gm/kg in 5 aliquots over 10 d period.

ROUTE AND SITE: Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

4584

COMPOUND: Phosphoric acid, di-p-tolyl o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: (1, 2 and 5) All had paralysis, (3) 1 had paralysis, (4) None had paralysis.

ANIMALS: 18 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.2 gm/kg
(2) 0.1 gm/kg
(3) 0.05 gm/kg
(4) 0.025 gm/kg
(5) 2.5 gm/kg in 5 aliquots over 10 d period.

ROUTE AND SITE: Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, di(3,5-xylyl) o-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

COMPOUND: Phosphoric acid, o-hydroxyphenyl phenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochemical Pharm. 15:541-548, 1966.

OBSERVED NEUROTOXIC EFFECTS: Weakened limbs. Histological changes in the spinal cord and sciatic nerves. Inhibition of CNS esterase.

ANIMALS: Hens, grps of 2-4, RIR x Light Sussex, 2-3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mostly 1 dose, amount varied by compound

ROUTE AND SITE: Oral, s.c., or i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 14-21 d

EXAM. TYPE: Biochemistry, histology

A39A

COMPOUND: Phosphoric acid, tolyl ester

REFERENCE: Smith, H.V. and Spalding, J.M.K.
Lancet 2: 1019-21, 1959.

OBSERVED NEUROTOXIC EFFECTS: Distal weakness and paresthesias. No deaths reported, most patients were expected to recover.

ANIMALS: Humans, more than 2,000 cases.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure via "olive oil" used in food preparation. Later exam. of sample showed oil to contain 3% mixed cresyl phosphates, mainly meta and para compounds.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Weeks

EXAM. TYPE: Behavior

410

COMPOUND: Phosphoric acid, o-tolyl ester

REFERENCE: Vora, D.D., Dastur, D.K., Braganca, B.M., Parihar, L.M., Iyer, C.G.S., Fodekar, R.B. and Prabhakaran, K.
J. Neurol. Neurosurg. Psychiat. 25: 234-242, 1962.

OBSERVED NEUROTOXIC EFFECTS: Glove-and-stocking type sensory impairment, distal muscle paralysis with characteristic gait; degeneration of intramuscular and intradermal nerve twigs, increased plasma cholinesterase.

ANIMALS: Human: 32 of 58 reported cases in Bombay in 1960.

PREPARATION AND DOSE or HISTORY OF PATIENT: History noncontributory. Later investigation showed that oil from some sources was contaminated with 0.65-32.5 mg OCP/100 g oil or with 2-12% of mineral oil containing OCP.

ROUTE AND SITE: Oral or skin contact (oil used for massaging body).

CONTROL INFORMATION: Epidemiological data

DURATION OF EXPERIMENT: Admissions over a 5-mo period

EXAM. TYPE: Clinical, lab, and histology of biopsy specimens.

COMPOUND: Phosphoric acid, triaryl ester

REFERENCE: Siegel, J., Rudolph, H.S., Getzkin, A.J. and Jones, R.A.
Tox. Appl. Pharm. 7: 543-549, 1965.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxic signs in chickens over 23 mg/m^3, in rabbits at 102 mg/m^3, but none in rats, dogs or monkeys at levels tested.

ANIMALS: 53 hens, White Vantress, 6 mo, 2-2 1/2 kg
50 rats, Long-Evans, 200-250 g
31 rabbits, NZ White, 3-4 kg
18 dogs, beagle, 6-10 kg
21 squirrel monkeys, 0.5-1 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 1.8-110 mg/m^3 of air, 24 hr/d, 36-163 d
(2) 25 and 50 mg/m^3 of air, 8 hr/d, 5 d/wk, total 30 exposures.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: 24 chickens, 30 rabbits, 10 monkeys

DURATION OF EXPERIMENT: Up to 1 yr after exposures

EXAM. TYPE: Behavior, autopsy (gross and histological)

COMPOUND: Phosphoric acid, tri(o-biphenylyl) ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

441

COMPOUND: Phosphoric acid, tributyl ester

000126738

REFERENCE: Chambers, H.W. and Casida, J.E.
Tox. Appl. Pharm. 10:105-118, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis; protection interpreted in terms of structure-activity relationships.

ANIMALS: Mice, Swiss albino, M, 14-17 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 850-1000 mg/kg
Study tested 71 nicotinic acid analogs for protection against neurotoxicity of compound.

ROUTE AND SITE: Mice: I.P.

CONTROL INFORMATION: Various parameters

DURATION OF EXPERIMENT: Up to 10 d

EXAM. TYPE: Clinical, biochemistry

442

COMPOUND: Phosphoric acid, triethyl ester

REFERENCE: Gumbmann, M.R., Gagne, W.E. and Williams, S.N.
Tox. Appl. Pharm. 12:360-371, 1968.

OBSERVED NEUROTOXIC EFFECTS: Adverse effects on growth (at 5%) and reproduction (at 1%), minimal changes in blood or brain cholinesterase (10% grp was excluded for anorexia), no brain changes reported.

ANIMALS: Rats, S-D, 5 M and 5 F/grp, initially 71-79 g, and their litters

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1-10% in diet.

ROUTE AND SITE: oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Original M killed at 120 d, F at 150 d.

EXAM. TYPE: Behavior, biochemistry, necropsy

COMPOUND: Phosphoric acid, tri-p-ethylphenyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

COMPOUND: Phosphoric acid, tri-p-ethylphenyl ester

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W. Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: Birds paralyzed with significant demyelination.

ANIMALS: 30 chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: 200 mg/kg - 5 x 500 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

443

COMPOUND: Phosphoric acid, tri-4-ethyl phenyl ester

REFERENCE: Cavanagh, J.B., Davies, D.R., Holland, P. and Lancaster, M. Porton Tech. Paper #760, 1961.

OBSERVED NEUROTOXIC EFFECTS: Threshold dose was "about" 150 mg/kg; between 150 and 500 mg/kg, signs were delayed till 20-30 d and preceded by typical "high stepping gait," followed by ataxia. Sciatic nerves always damaged severely, but ventral cord little. Relative absence of anticholinesterase.

ANIMALS: Hens, White Leghorn, ages 1-2 yr.

PREPARATION AND DOSE or HISTORY OF PATIENT: Triparethylphenylphosphate, TOCP, or diisopropyl-fluoridate at: (1) 150-750 mg/kg, (2) 30-400 mg/kg, (3) 0.3-1 mg/kg. (With Triparaethylphenylphosphate 500-1000 mg/kg ataxia and paralysis occur after 10-20 d and signs and results resemble those of TOCP and diisopropylfluoridate; aim of present study was to find threshold dose).

ROUTE AND SITE: I.M., breast muscle; oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 mo.

EXAM. TYPE: Behavior, histology

444

COMPOUND: Phosphoric acid, tri-o-ethylphenyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.0 gm/kg
(2) 2.5 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, triphenyl ester

000115866

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tritolyl ester

001330785

REFERENCE: Ahmed, M.M.
Acta Neuropath. 17:302-309, 1971.

OBSERVED NEUROTOXIC EFFECTS: Anterior horn of spinal cord examined. Synaptic vesicles and mitochondria of pre-synaptic bag were degenerated.

ANIMALS: 7 Hens, adult

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 ml painted on comb, one dose, to 4 hens.

ROUTE AND SITE: Topical, comb

CONTROL INFORMATION: 3 hens untreated.

DURATION OF EXPERIMENT: 3 wk

EXAM. TYPE: Histology

445

COMPOUND: Phosphoric acid, tritolyl ester

001330785

REFERENCE: Ahmed, M.M., and Glees, P.
Acta Neuropath. 19:94-98, 1971.

OBSERVED NEUROTOXIC EFFECTS: Ataxia and motor paralysis of hindlimbs. Large number of chromatolytic neurones in the lumbar segments of the spinal cord. Axonal degeneration in the long tracts and peripheral nerves.

ANIMALS: 4 Slow loris, adults, 218-360 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.2 ml/kg/d for 10 d to 3 animals.

ROUTE AND SITE: Topical, back of neck

CONTROL INFORMATION: One untreated animal.

DURATION OF EXPERIMENT: 11 wk.

EXAM. TYPE: Behavior; histology

446

COMPOUND: Phosphoric acid, tritolyl ester

001330785

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W.
Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: (1) Birds became ataxic. (2) Five birds became paralyzed, histological examination of one showed demyelination. (3) and (4) No adverse effects seen.

ANIMALS: (1) 2 Chickens (3) 1 Chicken
(2) 6 Chickens (4) 3 Chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: Ester contained only: m-cresol, p-cresol, 2:4 and 2:5 dimethylphenol.
(1) 250 mg/kg, daily for 2 d
(2) 500 mg/kg, two daily doses
(3) 2,500 mg/kg single dose of tri-m-tolyl phosphate
(4) As above, except tri-p-tolyl phosphate

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-m-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis reported.

ANIMALS: 6 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 5.0 gm/kg
(2) 1.0 gm/kg
(3) 5.0 gm/kg in 5 aliquots over 10 d period.

ROUTE AND SITE: Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

REFERENCE: Aldridge, W.N. and Barnes, J.M.
Biochem. Pharm. 6: 177-188, 1961.

OBSERVED NEUROTOXIC EFFECTS: Neurotoxicity independent of cholinesterase inhibition in vivo; the latter was found and attributed to some metabolite (unidentified). Little structure-activity relationship seen between triaryl phosphates. Most common sign of toxicity was ataxia.

ANIMALS: Chickens, F, aged over 4 mo, usually 6-12 mo, various breeds

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-5000 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24 hr to 21 d

EXAM. TYPE: Behavior

4477

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Baron, R.L., Bennett, D.R. and Casida, J.E.
Br. J. Pharmacol. 18:465-474, 1962.

OBSERVED NEUROTOXIC EFFECTS: Clinical and neurological comparison was made between this compound and its major cyclic phosphate metabolite. Ataxia was present with both, higher doses increased the degree of peripheral neuropathy. Axon and myelin damage was prominent with both agents.

ANIMALS: 14 Chickens, White Leghorn, aged 12-18 mo., av. 2 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1 ml/kg, one dose.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester (TOCP)

000078308

REFERENCE: Baron, R.L. and Casida, J.E.
Biochem. Pharm. 11: 1129-1136, 1962.

OBSERVED NEUROTOXIC EFFECTS: Ataxic doses inhibited selectively nerve esterases hydrolyzing butyryl esters of choline, glycerol and phenols. TOCP more persistent than metabolite. Oxidation of succinate, pyruvate, α-ketoglutarate by nerve and brain preparations was not affected.

ANIMALS: Chickens, White Leghorn, 1-2 y, 1.5-2.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: TOCP 1 ml/kg

ROUTE AND SITE: TOCP: gavage; DFP and metabolite: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Beresford, W.A. and Glees, P.
Acta Neuropath. 3: 108-118, 1963.

OBSERVED NEUROTOXIC EFFECTS: Paralysis; fiber degeneration in central nervous system (in cats only the cord was studied). Start: 9-14 d (hens), 3-4 wk (cats). Both ascending and descending degeneration is reported.

ANIMALS: 10 Hens, adult; 4 cats.

PREPARATION AND DOSE or HISTORY OF PATIENT: Hens: 0.2 ml/kg to 9 hens, 0.1 ml/kg to 1 hen, one dose.
Cats: 0.1 or 0.2 ml/d.

ROUTE AND SITE: Hens: Oral; Cats: Top. sk, neck

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr: hens 9-23d, cats 3-4 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Berry, J.F. and Cevallos, W.H.
J. Neurochem. 13: 117-124, 1966.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced demyelination with the following changes in lipid classes: increases in cholesterol esters, mono-or diglycerides, and lecithin; decrease in cerebrosides. Changes in fatty acid compositions of lipid classes were as follows: decrease of 15:0 and increase of 18:1 in cholesterol esters; increase of 16:0 in sphingomyelin; decrease of 22:0, 24:0, and 24:1 in cerebrosides; and decrease of 18:0 in phosphotidylserine.

ANIMALS: Chickens, not further described
Chicken nerves from NMRI, Bethesda

PREPARATION AND DOSE
or HISTORY OF PATIENT: Aerosols, not measured.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Untreated

DURATION OF EXPERIMENT: Onset of paralysis, usually 2 wk

EXAM. TYPE: Biochemistry

449<

COMPOUND: Phosphoric acid, tri-o-tolyl ester

REFERENCE: Bischoff, A.
Acta Neuropath. 9:158-174, 1967.

OBSERVED NEUROTOXIC EFFECTS: Weakness on standing appeared by 10-14 d, then paralysis of extensors and toes, progressed 4-6d then ceased. Axoplasm of sciatic nerves with moderate damage to myelin: neurolfilaments and endoplasmic reticulum distorted. Unmyelinated nerves also affected. Severity of the disease is the same on all levels of the peripheral nerves. There is an evident proportional correlation between the severity of morphological alterations and severity of clinical symptoms.

ANIMALS: 24 Chickens, Leghorn and sexlinked cross Rhode Island Red/Barred Plymouth Rock, aged 6 and 12 wk.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5-1 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Age-matched untreated controls.

DURATION OF EXPERIMENT: Sacr 1-20 d after first appearance of neuropathology

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Bischoff, A.
Acta Neuropath. 15:142-155, 1970.

OBSERVED NEUROTOXIC EFFECTS: Slight but definite paralysis of distal leg muscles. Diseased axons in the white matter of spinal cord: proliferation of endoplasmic reticulum and disintegration of neurofilaments. Severe structural alterations in the boutons terminaux in grey substance of the anterior horn; swelling of axosomatic synapses.

ANIMALS: 16 chickens, Leghorn and sexlinked cross Rhode Island Red/Barred Plymouth Rock, aged 8 wk.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5-1 ml/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Breed-matched untreated controls.

DURATION OF EXPERIMENT: Sacr d 1, 6 and 14 after first neurological signs.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Cavanagh, J.B
J. Path. Bact. 87: 365-383, 1964

OBSERVED NEUROTOXIC EFFECTS: Ataxia, abnormal gait and Wallerian degeneration in peripheral nerves. Axonal and Myelin sheath fragmentation. Distal degeneration of sensory nerve endings.

ANIMALS: Cats: young F and castrated M of known parentage.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.01-0.75 mg/kg as oil

ROUTE AND SITE: S.C., flank

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Maximum 17 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Cavanagh, J.B. and Patangia, G.N.
Brain 88: 165-181, 1965

OBSERVED NEUROTOXIC EFFECTS: Weakness and ataxia in hind limbs. "Dying back" process in long pathway nerve fibers. Degeneration in long ascending and descending spinal tracts. Axonal degeneration with swelling, increased argyrophilia, eosinophilic change and fragmentation. Degeneration in spino cerebellar tract above C.7 spinal level.

ANIMALS: Cats: young F and castrated M of known parentage.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.01-0.75 mg/kg as oil

ROUTE AND SITE: S.C., flank

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Maximum 17 wk

EXAM. TYPE: Behavior, histology

451

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Chambers, H.W. and Casida, J.E.
Tox. Appl. Pharm. 10:105-118, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis; protection interpreted in terms of structure-activity relationships.

ANIMALS: Adult hens, 1.5-2.5 kg.
Mice, Swiss albino, M, 14-17 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Hens: 0.5 ml/kg
Mice: 50 mcl/mouse
Study tested 21 nicotinic acid analogs for protection against neurotoxicity of compounds.

ROUTE AND SITE: Hens: gavage. Mice: I.P.

CONTROL INFORMATION: Various parameters

DURATION OF EXPERIMENT: Up to 10 d

EXAM. TYPE: Clinical, biochemistry

4527

COMPOUND: Phosphoric acid, tri-o-tolyl ester

REFERENCE: Glees, P. and Janzik, H.
Progr. Brain Res. 14:97-121, 1965.

OBSERVED NEUROTOXIC EFFECTS: Flaccid paralysis and death (LD study). Ascending and descending nerve fiber degeneration especially in the reticulo-cerebellar systems.

ANIMALS: Chicks (not fully described)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1-0.2 ml/kg

ROUTE AND SITE: Topical (comb)

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Follow-up for 5.5 mo.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Glees, P. and White, W.G.
J. Neurol. Neurosurg. Psychiat. 24: 271-274, 1961.

OBSERVED NEUROTOXIC EFFECTS: Characteristic paralysis of leg extensors with 0.1 ml/kg. Selected cord degeneration of myelin and axons; even one dose of 0.05 ml/kg caused some degeneration in anterior medial tract; no peripheral nervous system (leg) degeneration seen at these dosages.

ANIMALS: 40 mature hens and cocks, 3-5 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: Up to (1) 0.2 ml/bird, one or more doses at day-intervals
(2) 0.1-0.3 ml/kg orally

ROUTE AND SITE: (1) Painted on comb, (2) oral.

CONTPOL INFORMATION: ns

DURATION OF EXPERIMENT: About 2 mo.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: Paralysis seen in all groups.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.4 gm/kg, 0.8 gm/kg
(2) 0.2 gm/kg
(3) 0.1 gm/kg
(4) 0.05 gm/kg
(5) 0.025 gm/kg
(6) 2.5 gm/kg in 5 aliquots over 10 d period

ROUTE AND SITE: Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

453<

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Illis, L., Patangia, G.N. and Cavanagh, J.B.
Exp. Neurol. 14:160-174, 1966.

OBSERVED NEUROTOXIC EFFECTS: Changes in boutons terminaux corresponded with onset of ataxia, more pronounced in lumbar than in cervical cord segments. Changes occurred mainly in intermediate greymatter. Preterminal degeneration started 5 d after onset of ataxia.

ANIMALS: 6 cats, M & F, 1.5-3.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-0.25 mg/kg

ROUTE AND SITE: S.C.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 8-327 d

EXAM. TYPE: Histology

454

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: LeVay, S., Meier, C. and Gleas, P.
Acta Neuropath. 17:103-113, 1971.

OBSERVED NEUROTOXIC EFFECTS: Neurological symptoms appeared after 8 d. After 6 d about 25% of the large myelinated fibers of peripheral nerves contained an abnormal system of membranous tubules and vacuoles; degeneration progressed. Membranous proliferation was followed 4-9 d later by massive changes in the spinal ganglia; by a hypertrophy of the endoplasmic reticulum in some cells and of neurofilaments in others.

ANIMALS: 9 Hens, White Leghorn, Adult.

PREPARATION AND DOSE or HISTORY OF PATIENT: 6 Hens given 2 ml/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 3 untreated

DURATION OF EXPERIMENT: Serial sacr 6-16 d

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Prineas, J.
J. Neuropath. Exp. Neurol. 28(4):571-597, 1969.

OBSERVED NEUROTOXIC EFFECTS: Progressive weakness, impaired tail response, ataxia, Electronmicroscopical peripheral nervous system changes preceded behavior or photomicroscopical changes, in motor nerve terminals; small myelinated fibers of spinal gray matter also affected. Then neuromuscular junctions and anterior horns showed changes in endoplasmic reticulum. Demyelination starting distally always along with other degenerative changes. Described as dying-back polyneuropathy.

ANIMALS: 18 Cats, M and F, young and old, 2.25-5.75 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5-3.0 ml/kg, TOCP 99% pure (impurities were mixed esters of phenol and orthocresol).

ROUTE AND SITE: S.C., left thigh

CONTROL INFORMATION: 4 cats, treatment n.s.

DURATION OF EXPERIMENT: 42 d

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Taylor, J.D.
Can. J. Physiol. Pharm. 43: 715-721, 1965.

OBSERVED NEUROTOXIC EFFECTS: Demyelination, verified histologically, was found in cervical and caudal cord sections to involve increases of phospholipid content and of the phosphatidylethanolamine fraction of phospholipids (proportion of other fractions unaltered). The increase was shown to involve synthesis.

ANIMALS: Cats, adult M

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.4 ml/kg in peanut oil
Slices of spinal cord from treated cats in incubation system

ROUTE AND SITE: I.M., left forelimb

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Average 8 d plus in vitro studies

EXAM. TYPE: Biochemistry

455A

COMPOUND: Phosphoric acid, tri-o-tolyl ester

000078308

REFERENCE: Vij, S. and Kanagasuntheram, R.
Acta Neuropath. 20:150-159, 1972.

OBSERVED NEUROTOXIC EFFECTS: Unsteady movements. Most notable finding in afferent nerve endings dealt with cholinesterase activity: reduction of specific activity, almost complete absence of non-specific activity. Degeneration of taste bud cells, and degenerative changes in the sensory nerve terminations.

ANIMALS: Slow loris, 2 adult, one "very young"

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.25 ml applied every 4th day for 12 applications (1 adult, 1 young). Other adult given 0.25 ml oral, one dose.

ROUTE AND SITE: Topical, back of neck; oral.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Maximum survival 50 d.

EXAM. TYPE: Behavior, histology, histochemistry

456

COMPOUND: Phosphoric acid, tri-p-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.H. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 6 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 5.0 gm/kg
(2) 1.0 gm/kg
(3) 5.0 gm/kg given in 5 aliquots over 10 d period.

ROUTE AND SITE: Per os.

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, trixylyl ester

REFERENCE: Bondy, H.F., Field, E.J., Worden, A.N. and Hughes, J.P.W.
Brit. J. Indust. Med. 17: 190-200, 1960.

OBSERVED NEUROTOXIC EFFECTS: Four of twelve birds developed ataxia.

ANIMALS: 12 Chickens

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 x 500 mg/kg

ROUTE AND SITE: Gavage

CONTROL INFORMATION: Controls mentioned but not described.

DURATION OF EXPERIMENT: Up to 1 yr

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-2,4-xylyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.0 gm/kg
(2) 2.5 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

457<

COMPOUND: Phosphoric acid, tri-2,5-xylyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.0 gm/kg
(2) 2.5 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

458

COMPOUND: Phosphoric acid, tri-2,6-xylyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.0 gm/kg
(2) 2.5 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphoric acid, tri-3,5-xylyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 4 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phosphorochloridic acid, di-o-tolyl ester

REFERENCE: Hine, CH., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: No paralysis.

ANIMALS: 8 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 0.5 gm/kg
(2) 1.0 gm/kg
(3) 2.5 gm/kg in 5 aliquots over 10 d period.

ROUTE AND SITE: Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

459

COMPOUND: Phosphorochloridous acid, bis(3,5-xylyl)ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: Anticholinesterase effects studied in vivo and in vitro. No cholinesterase inhibition in fowl plasma, however compound was active against the enzymes of human plasma.

ANIMALS: (1) 5 Cockerels (2) Human erythrocytes and plasma

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 1 gm/kg.
(2) Laboratory method, no details.

ROUTE AND SITE: (1) Oral (2) In vitro

CONTROL INFORMATION: (1) 5 untreated birds

DURATION OF EXPERIMENT: (1) 24 hr.

EXAM. TYPE: Biochemical

460

COMPOUND: Phosphorodiamidic fluoride, N,N'-dibutyl-

REFERENCE: Johnson, M.K. and Barnes, J.M.
Biochem. Pharm. 19:3045-3047, 1970.

OBSERVED NEUROTOXIC EFFECTS: 4 or 5 doses (0.2 mg/kg) produced marginal response. 6 doses resulted in frequent collapse and inability to stand. Regression occurred rapidly in chicks, slowly in adults. Severely ataxic chicks had characteristic lesions in both peripheral nerve and spinal cord.

ANIMALS: Chickens, various breeds, sex not stated.

PREPARATION AND DOSE or HISTORY OF PATIENT: Vehicle: 10% ethanol, various schedules, premedication with atropine or eserine.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: Up to 63 d.

EXAM. TYPE: Behavior, then histology. Also, in vitro bioassay.

COMPOUND: Phosphorodichloridic acid, o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: All died.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg.
(2) 1.0 gm/kg.

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND:
Phosphorodithioic acid, S,S'-benzylidene bis-O,O-dimethyl

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 5096 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

461

COMPOUND: Phosphorodithioic acid, S,S'-benzylidene O,O,O',O'-tetramethyl ester
002782709

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 300 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

462

COMPOUND: Phorphorodithioic acid, bis(4-chlorophenyl)methyl-O,O-diethyl

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.
Acute: Chicks appeared normal until 6 days post treatment, then leg paralysis lasting up to 5 days. The highest dosage levels given resulted in only 30% mortality. Significant growth depression even at levels lower than the LD_{50}.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} > 3000 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphorodithioic acid, S-(p-chlorophenyl)thio methyl O,O-diethyl ester

000786196

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 640 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, S-(((p-chlorophenyl)thio) methyl) 0,0-diethyl ester

000786196

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 57.2 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

463>

COMPOUND: Phosphorodithioic acid, S-(((p-chlorophenyl)thio)methyl) 0,0-dimethyl ester

000953173

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 800 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

464

COMPOUND: Phosphorodithioic acid, S(((p-chlorophenyl)thio)methyl)0,0-dimethyl ester

000953173

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Chicks were highly excitable and exhibited a "flying" syndrome at lower dose levels. After several hours syndrome was followed by paralysis and dehydration of leg tissue. Compound caused death over a 2-day period. (2) 50% cholinesterase inhibition by dose of >800 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (544.3 mg/kg) in gelatin capsule, 4-5 dose levels used.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

COMPOUND: Phosphorodithioic acid, S-((4,6-diamino-S-triazin-2-yl)methyl)0,0-dimethyl ester

000078579

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 600 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, S-(((2,5-dichlorophenyl)thio)methyl) 0,0-diethyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.
Acute: the highest dosage levels given resulted in only 20% mortality.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} > 5000 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

465>

COMPOUND: Phosphorodithioic acid, (((3,4-dichlorophenyl)thio)methyl) 0,0-diethyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 143.0 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

466

COMPOUND: Phosphodithioic acid, S-((3,4-dichlorophenylthio)methyl) O,O-dimethyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 693.7 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphorodithioic acid, O,O-diethyl ester, S,S-diester with p-dioxane-2,3-dithiol

000078342

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 320 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, 0,0-diethyl ester, S-ester with 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3H)one

002642719

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 34.4 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

467

COMPOUND: Phosphorodithioic acid, 0,0-diethyl S-(2 ethylthio)ethyl)ester

000298044

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: >50 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

468

COMPOUND: Phosphorodithioic acid, 0,0-diethyl S-(2 ethylthio)ethyl) ester

000298044

REFERENCE: Redhead, I.H.
Lancet 1: 686-688, 1968.

OBSERVED NEUROTOXIC EFFECTS: The subject experienced headaches, nausea and dizziness. Clinical examination showed abnormally low cholinesterase.

ANIMALS: Human, M, 48 yr

PREPARATION AND DOSE
or HISTORY OF PATIENT: Occupational exposure to dimeton and disulfoton for 5 yr

ROUTE AND SITE: Inhalation, topical

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 5 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, 0,0-diethyl S-(ethylthio)methyl ester

000298022

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 48 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-(2-methoxyacetyl) acetamide

000919766

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 94.0 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

469>

COMPOUND: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-methylacetamide (Dimeton)

000060515

REFERENCE: Redhead, I.H.
Lancet 1: 686-688, 1968.

OBSERVED NEUROTOXIC EFFECTS: The subject experienced headaches, nausea and dizziness. Clinical examination showed abnormally low cholinesterase.

ANIMALS: Human, M, 48 yr

PREPARATION AND DOSE
or HISTORY OF PATIENT: Occupational exposure to dimeton and disulfoton for 5 yr

ROUTE AND SITE: Inhalation, topical

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 5 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, O-O-dimethyl ester, S-ester with 3(mercaptomethyl)-1,2,3-benzotriazin-4(3H)-one
000086500

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 150 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 3-(mercapto-methyl)-1,2,3 benzotriazin-4(3H)-one
000086500

REFERENCE: Murphy, S.D., Lauwerys, R.R. and Cheever, K.L.
Tox. Appl. Pharm. 12: 22-35, 1968.

OBSERVED NEUROTOXIC EFFECTS: Poor inhibitor of brain cholinesterase.
Metabolized to Gutoxon which is an inhibitor.

ANIMALS: Mice, Swiss-Webster, M, 25-30g
Chickens, White Rock X N.H. Red, M, 500-700g
Sunfish, M and F, 40-80g
Bullfish, M and F, 40-80g
In vitro brains of rats, guinea pigs, sparrows, smallmouth bass, flounder, sculpin and monkey.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1-1500 mg/kg, various schedules (I.P.) in mice, chickens, sunfish and bullheads; 0.1-200 mg/kg (orally) in sunfish; 0.001-4 picomoles of malaoxon *in vitro*.

ROUTE AND SITE: See above

CONTROL INFORMATION: Brain cholinesterase determined in controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry

COMPOUND: Phosphorodithioic acid, 0,0-dimethyl ester, S-ester with 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3H)-one

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y. Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 277.2 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

471

COMPOUND: Phosphorodithioic acid, 0,0-dimethyl ester, S-ester with N-(mercaptomethyl) phthalimide
000732116

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Caused death within 18 hrs, any survivors lethargic or paralyzed for as long as 2 d post treatment. (2) 50% cholinesterase inhibition by dose of 400 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (707.0 mg/kg) in gelatin capsule.
(2) Subacute: LD_{50} 50-800 ppm in diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

COMPOUND: Phosphorodithioic acid, O-ethyl S, S-dipropyl ester

013194484

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y. Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 5.5 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphorodithioic acid, S,S'-methylene O,O,O',O'-tetraethyl ester

000563122

REFERENCE: Comstock, E.G., Bickel, L., and McCormick, R.A., Jr. Texas Medicine 63: 71-75, 1967.

OBSERVED NEUROTOXIC EFFECTS: Generalized flaccid paralysis and areflexia; respiratory distress.

ANIMALS: Human, M, 6 mo.

PREPARATION AND DOSE or HISTORY OF PATIENT: 15.7 mg/kg

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND. Phosphorodithioic acid, S,S'methylene 0,0,0',0'-tetraethyl ester

000563122

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 1200 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

473

COMPOUND: Phosphonodithioic acid, methyl-, O-phenyl S-propyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 8.1 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

474

COMPOUND: Phosphorofluoridic acid, bis(1-methylethyl) ester

000055914

REFERENCE: Baron, R.L. and Casida, J.E.
Biochem. Pharm. 11: 1129-1136, 1962.

OBSERVED NEUROTOXIC EFFECTS: Ataxic doses inhibited selectively nerve esterases hydrolyzing butyryl esters of choline, glycerol and phenols. TOCP more persistent than metabolite. Oxidation of succinate, pyruvate, α-ketoglutarate by nerve and brain preparations was not affected.

ANIMALS: Chickens, White Leghorn, 1-2 y, 1.5-2.5 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2mg/kg

ROUTE AND SITE: TOCP: gavage; DFP and metabolite: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry

COMPOUND: Phosphorofluoridic acid, bis(1-methylethyl) ester

000055914

REFERENCE: Johnson, M.K. and Barnes, J.M.
Biochem. Pharm. 19:3045-3047, 1970.

OBSERVED NEUROTOXIC EFFECTS: 1 mg/kg in hens aged 12 mo or more caused frequent collapse and inability to stand. 2-5 mg/kg in chicks aged 7-49 d produced no effect, but given at 60-130 d was increasingly toxic. Repeated doses produced ataxia and "characteristic" lesions in cord and peripheral nerves.

ANIMALS: Chickens, various breeds, sex not stated.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 ml/kg, then 0.1 ml/kg up to 6 doses.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: Up to 63 d.

EXAM. TYPE: Behavior, then histology. Also, in vitro bioassay.

COMPOUND: Phosphorofluoridic acid, methyl-,isopropyl ester (Sarin)

000107448

REFERENCE: Grob, D. and Johns, R.J.
Neurology 8: 897-902, 1958.

OBSERVED NEUROTOXIC EFFECTS: Overdoses of sarin resulted in neuromuscular block from cholinesterase inhibition; partly relieved by certain oximes.

ANIMALS: Human: "many instances"

PREPARATION AND DOSE
or HISTORY OF PATIENT: Patients with myasthenia medicated with compound, doses ns.

ROUTE AND SITE: Probably intraarterial

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Electrophysiology, clinical.

475

COMPOUND: Phosphorothioic acid, O-(2-(sec-butoxymethylthio)ethyl) O,O-diethyl ester

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed by death within 18 hr. Survivors were lethargic for 6-19 hrs post treatment.
(2) 50% cholinesterase inhibition by dose 280 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} (28.6 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

476

COMPOUND: Phosphorothioic acid, O-(2-chloro-1-(2,4-dichlorophenyl) vinyl O,O-dimethyl ester

REFERENCE: Morallo, B.D. and Sherman, M.
J. Econ. Entomol. 60:509-515, 1967.

OBSERVED NEUROTOXIC EFFECTS: The order of resistance to the insecticide was: flesh fly > house fly > anthomyiid fly > blow fly. This insecticide is a relatively rapid toxicant with 50% mortality occurring within 1 hour for blow flies and house flies and within 4 hours for the other two flies. There was significant inhibition of cholinesterase in house flies and flesh flies, but had little effect on the others. Recovery was just about complete in 24 hours. Dead flies showed more pronounced effects than living flies.

ANIMALS: Housefly, Musca domestica, adult F, 3-4 d old
Anthomyiid fly, Fannia pusio, adult F, 3-4 d old
Blowfly, Chrysoma megacephala, adult F, 3-4 d old
Flesh fly, parasarcophaga argyrostoma, adult F, 3-4 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: The LD_{50} (0.26-21.6 mcg/g), 10-20 flies/group or dose-level, each test replicated 3 or more times.
In vivo: 10 groups of 50 each of houseflies and anthomyiid flies, and 10 groups of 20 each of blowflies and flesh flies.

ROUTE AND SITE: Applied topically, venter of thorax.

CONTROL INFORMATION: Untreated fly heads

DURATION OF EXPERIMENT: Serial to 24 hr.

EXAM. TYPE: Biochemistry, mortality

COMPOUND: Phosphorothioic acid, O-(2-chloro-4-nitrophenyl) O,O-dimethyl ester

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 300 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorothioic acid, O-(p-cyanophenyl) O,O-dimethyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 23.5 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

4776

COMPOUND: Phosphorothioic acid, O-(2,4-dichlorophenyl)-O,O-diethyl ester

000097176

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 148.2 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

478

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(2-isopropyl-6-methyl-4-pyrimidinyl) ester

000333415

REFERENCE: Rayner, M.D., Popper, J.S., Carvalho, E.W. and Hurov, R. Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE: Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

COMPOUND: Phosphorothioic acid, 0,0-diethyl-0-(4-(methylthio)-3,5-xylyl) ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y. Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 17.9 mg/kg
(2) Subacute: ^{50}50-800 ppm in diet, 20 chicks/grp, for 3 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester

REFERENCE: McFarland, L.Z. and Lacy, P.B.
Tox. Appl. Pharm. 12:105-114, 1968.

OBSERVED NEUROTOXIC EFFECTS: Death in 30 min to 2 hr. Salivation, tremors, clonic convulsions and ataxia. (Parasympathomimetic responses.)

ANIMALS: (1) 46 Japanese quail, adult
(2) 7 Pintail ducks, adult
(3) 36 Mallard ducks, adult

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 3.9-5.7 mg/kg
(2) 1.6-2 mg/kg
(3) 0.6-1.7 mg/kg

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 2 hr.

EXAM. TYPE: Behavior, physiology

4796

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester

000056382

REFERENCE: Murphy, S.D., Lauwerys, R.R. and Cheever, K.L.
Tox. Appl. Pharm. 12: 22-35, 1968.

OBSERVED NEUROTOXIC EFFECTS: Poor inhibitor of brain cholinesterase. Metabolized to paraoxon which is an inhibitor.

ANIMALS: Mice, Swiss-Webster, M, 25-30g
Chickens, White Rock X N.H. Red, M, 500-700g
Sunfish, M and F, 40-80g
Bullfish, M and F, 40-80g
In vitro brains of rats, guinea pigs, sparrows, smallmouth bass, flounder, sculpin and monkey.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-1500 mg/kg, various schedules (I.P.) in mice, chickens, sunfish and bullheads; 0.1-200 mg/kg (orally) in sunfish; 0.001-4 picomoles of malaoxon in vitro.

ROUTE AND SITE: See above

CONTROL INFORMATION: Brain cholinesterase determined in controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry

480

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester

000056382

REFERENCE: Rayner, M.D., Popper, J.S., Carvalho, E.W. and Hurov, R.
Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE: Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) ester

002921882

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 200 mg/kg produced leg weakness, delayed 3-18 days after dosing

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compoun graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) ester

00 121882

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 25.4 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

481<

COMPOUND: Phosphorothioic acid, 0,0-diethyl 0-1,2,2-trimethyl propyl ester

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hr. Survivors were lethargic for 6-19 hrs. post treatment. (2) 50% cholinesterase inhibition by doses of >800 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (1633.0 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

482

COMPOUND: Phosphorothioic acid, O,O-diisopropyl O-(4-methylsulfinyl phenyl) ester

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hrs. Survivors were lethargic for 6-19 hrs post treatment.
(2) 50% cholinesterase inhibition by doses of 90 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (32.6 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

947

COMPOUND: Phosphorothioic acid, O,O-dimethyl ester, O,O-diester with 4,4'-thiodiphenol

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14:515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 1000 mg/kg produced leg weakness.

ANIMALS: Chickens, White Leghorn, F.

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min. prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 1 yr.

EXAM. TYPE: Clinical

948

COMPOUND: Phosphorothioic acid, O,O-dimethyl S-(2-(ethylsulfinyl) ethyl) ester

REFERENCE: Sherman, H., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hrs. Survivors were lethargic 6-19 hr post treatment.
(2) 50% cholinesterase inhibition by dose of >800 ppm.

ANIMALS: Cockarels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (79.6 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

4823

COMPOUND: Phosphorothioic acid, O,O-dimethyl S-(2-(ethylsulfonyl)ethyl) ester

REFERENCE: DuBois, K.P and Plzak, G.J.
Tox. Appl. Pharm. 4: 621-630, 1962.

OBSERVED NEUROTOXIC EFFECTS: Inhibited brain cholinesterase in vitro. Sublethal doses inhibited cholinesterase of central nervous system and peripheral nervous system in vitro.

ANIMALS: Rats, S-D, M and F, 200-275g
Mice, CF_1, adult M and F
Guinea pigs, young M, 200-300g

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50} and other schedules

ROUTE AND SITE: Oral, I.P., skin contact

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Up to 72 hr

EXAM. TYPE: Biochemistry

4847

COMPOUND: Phosphorothioic acid, 0,0-dimethyl S-(2-ethylthioethyl) ester

REFERENCE: DuBois, K.P and Plzak, G.J.
Tox. Appl. Pharm. 4: 621-630, 1962.

OBSERVED NEUROTOXIC EFFECTS: Inhibited brain cholinesterase in vitro. Sublethal doses inhibited cholinesterase of central nervous system and peripheral nervous system in vitro.

ANIMALS: Rats, S-D, M and F, 200-275g
Mice, CF_1, adult M and F
Guinea pigs, young M, 200-300g

PREPARATION AND DOSE
or HISTORY OF PATIENT: LD_{50} and other schedules

ROUTE AND SITE: Oral, I.P., skin contact

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Up to 72 hr

EXAM. TYPE: Biochemistry

COMPOUND: Phosphorothioic acid, 0,0-dimethyl S-(2-(isopropylsulfino) ethyl) ester

REFERENCE: DuBois, K.P and Plzak, G.J.
Tox. Appl. Pharm. 4: 621-630, 1962.

OBSERVED NEUROTOXIC EFFECTS: Inhibited brain cholinesterase in vitro. Sublethal doses inhibited cholinesterase of central nervous system and peripheral nervous system in vitro.

ANIMALS: Rats, S-D, M and F, 200-275g
Mice, CF_1, adult M and F
Guinea pigs, young M, 200-300g

PREPARATION AND DOSE
or HISTORY OF PATIENT: LD_{50} and other schedules

ROUTE AND SITE: Oral, I.P., skin contact

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Up to 72 hr

EXAM. TYPE: Biochemistry

COMPOUND: Phosphorothioic acid, 0,0-dimethyl O-(p-methylsulfinyl)phenyl) ester

000115913

REFERENCE: Sherman, H., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsion followed in many by death within 18 hr. Survivors were lethargic for 6-19 hr post treatment. (2) 50% Cholinesterase inhibition by dose of >800 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (2.32 mg/kg) in gelatin capsule.
(2) Subacute: $^{50}_{50}$-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

485

COMPOUND: Phosphorothioic acid, 0,0-dimethyl-,O-(4-methylthio)-m-tolyl) ester (DMTP)

000055389

REFERENCE: DuBois, K.P. and Kinoshita, F.
Tox. Appl. Pharm. 6: 86-95, 1964.

OBSERVED NEUROTOXIC EFFECTS: Brain anticholinesterase inhibited for prolonged periods, exposures cumulative, toxicity potentiated by combination with 2,3-p-dioxanedithiol-S,S-bis-(O,O-diethyl phosphorodithioate) (Delnav) or O,O-diethyl O-3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphorothioate (Co-Ral), or Malathion.

ANIMALS: Rats, S-D, M and F, 175-275 g
Guinea pigs, M, 200-300 g
Mice, CF_1, adult M and F

PREPARATION AND DOSE or HISTORY OF PATIENT: In diet: 1% (mice) or 0.1% (rats, guinea pigs) of body weight; I.P.: 10-100 mg/kg (rats); Topical: up to 500 mg/kg DMTP + other compounds, equitoxic combinations.

ROUTE AND SITE: Oral (diet), I.P., topical (shaved back, rats)

CONTROL INFORMATION: Zero doses

DURATION OF EXPERIMENT: Up to 60 d

EXAM. TYPE: Mortality, behavior, biochemistry

COMPOUND: Phosphorothioic acid, 0,0-dimethyl-,0-(4-methylthio)-m-tolyl) ester

000055389

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 40 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorothioic acid, 0,0-dimethyl 0-(4-methylthio)-3,5-xylyl) ester

000055378

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 102.8 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 3 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

COMPOUND: Phosphorothioic acid, 0,0-dimethyl-0-(p-nitrophenyl)ester

000298000

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 200 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

4872

COMPOUND: Phosphorothioic acid, 0,0-dimethyl 0-(4-nitro-m-tolyl) ester

000122145

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Acute: LD_{50} 279.5 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

4887

COMPOUND: Phosphorothioic acid, O,O-dimethyl S-((4-oxo-1,2,3-benzotriazin-3(4H)-yl)methyl) ester
000961228

REFERENCE: Murphy, S.D., Lauwerys, R.R. and Cheever, K.L.
Tox. Appl. Pharm. 12: 22-35, 1968.

OBSERVED NEUROTOXIC EFFECTS: Inhibits brain cholinesterase.
Sensitivities: fish > mammals > birds.

ANIMALS: Mice, Swiss-Webster, M, 25-30g
Chickens, White Rock X N.H. Red, M, 500-700g
Sunfish, M and F, 40-80g
Bullfish, M and F, 40-80g
In vitro brains of rats, guinea pigs, sparrows, smallmouth bass, flounder, sculpin and monkey.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-1500 mg/kg, various schedules (I.P.) in mice, chickens, sunfish and bullheads; 0.1-200 mg/kg (orally) in sunfish; 0.001-4 picomoles of malaoxon in vitro.

ROUTE AND SITE: See above

CONTROL INFORMATION: Brain cholinesterase determined in controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry

COMPOUND: Phosphorothioic acid, O-O-dimethyl O(2,4,5-trichlorophenyl) ester
000299843

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 1600 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorotrithioic acid, O-methyl S,S-dipropyl ester

REFERENCE: Sherman, M., Herrick, R.B., Ross, E. and Chang, M.T.Y.
Toxicol. Appl. Pharm. 11: 49-67, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, paralysis, convulsions.
Acute: Significant growth depression even at levels lower than the LD_{50}.

ANIMALS: Cockerels, Single Comb White Leghorn, 10-12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} 9.6 mg/kg
(2) Subacute: 50-800 ppm in diet, 20 chicks/grp, for 2 wk

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated control grps

DURATION OF EXPERIMENT: 1-3 wk

EXAM. TYPE: Behavior, mortality

489

COMPOUND: Phosphorotrithioic acid, S,S,S-tributyl ester

000078488

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 200 mg/kg produced leg weakness, delayed 14-24 days after dosing

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

490

COMPOUND: Phosphorotrithious acid, tributyl ester

000150505

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 600 mg/kg produced leg weakness, delayed 3-21 days after dosing

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Phosphorous acid, tri-o-tolyl ester

REFERENCE: Hine, C.H., Dunlap, M.K., Rice, E.G., Coursey, M.M., Gross, R.M. and Anderson, H.H.
J. Pharm. Exp. Ther. 116:227, 1956.

OBSERVED NEUROTOXIC EFFECTS: All died.

ANIMALS: 22 Chickens, White Leghorn, M, 0.75-1.3 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.5 gm/kg
(2) 1.0 gm/kg

ROUTE AND SITE: (1) S.C. (2) Oral

CONTROL INFORMATION: One group of 5 per experimental group.

DURATION OF EXPERIMENT: 14-36 d after treatment.

EXAM. TYPE: Behavior, histology

COMPOUND: Phthalate plasticizers (mixture)

REFERENCE: Milkov, L.E., Aldyreva, M.V., Popova, T.B., Lopukhova, K.A., Malarenko, Y.L., Malyar, L.M. and Shakhova, T.K. Env. Hlth. Persp. 3:175-178, 1973. (Trans from Gig. Trud. 13:14, 1969).

OBSERVED NEUROTOXIC EFFECTS: Limb weakness and sensory disturbance after 6-7 yr exposure, progressive. Polyneuritis (32 in autonomic nervous system, 15 mixed), function disturbed in 22. High pain threshold in 66.7%, low sensitivity to vibrations in 33.8%, 78% of 81 subjects examined for vestibular disorder had it, 82% olfactory changes, no auditory disturbances.

ANIMALS: 147 Humans, 60 M and 87 F, 75% younger than 40.

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to mixture of compounds, levels of mixed esters 10-66 mg/m^3. 54 exposed 0.5-5 yr, 28 for 6-10 yr and 28 for 10-19 yr.

ROUTE AND SITE: Inhalation, skin contact

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Survey, electrophysiology, clinical, biochemical.

491

COMPOUND: Phthalimide,N-(2,6-dioxo-3-piperidyl)-

000050351

REFERENCE: McBride, W.G. Teratology 10:283-292, 1974.

OBSERVED NEUROTOXIC EFFECTS: Fetal spinal ganglia were examined. Treated group produced: 37 normals, 7 with reduction deformities, 49 resorptions; control group; 22 normals, no deformities. Dorsal root ganglia of the deformed fetuses showed degenerative changes particularly in the cervical and lumbar regions of the cord. Reduction in number of sensory neurons, believed to be causative of, or consequent to, the reduction deformities of the forelimbs.

ANIMALS: Rabbits, NZ White, F, 3.5-5 kg, pregnant.

PREPARATION AND DOSE or HISTORY OF PATIENT: 90-1000 mg/kg/d from d 7, 8, or 11 of pregnancy.

ROUTE AND SITE: Oral; gavage or capsule

CONTROL INFORMATION: Untreated controls

DURATION OF EXPERIMENT: 29 d

EXAM. TYPE: Teratological

492

COMPOUND: Phthalimide, N-(2,6-dioxo-3-piperidyl)-

000050351

REFERENCE: McCredie, J. and McLeod, J.G.
Lancet ii:1111 (1974)

OBSERVED NEUROTOXIC EFFECTS: Immature ganglion strucutre vs. mature in controls, resembling human fetus at 3-4 mo., interpreted as developmental arrest of embryonic dorsal-root ganglia. Concluded that reduction deformities are due to embryonic sensory neuropathy, caused by compound.

ANIMALS: Rabbits, newborn, of dams treated with compound.

PREPARATION AND DOSE or HISTORY OF PATIENT: Amt to dams ns.

ROUTE AND SITE: ns.

CONTROL INFORMATION: Matched untreated controls

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology

COMPOUND: Phthalimide, N-hydroxy-,O-ethyl O-isopropyl phosphorothioate

003733844

REFERENCE: Sherman, M., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hr. Survivors were lethargic for 6-19 hrs. post treatment. (2) 50% cholinesterase inhibition by dose of 150 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (111.1 mg/kg) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

COMPOUND: Picolinic acid, 5-amino-6-(7-amino-5,8-dihydro-6-methoxy-5,8-dioxo-2-quinolyl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methyl

003930196

REFERENCE: Warkany, J. and Takacs, E.
Arch. Path. 79(1):65-79, 1965.

OBSERVED NEUROTOXIC EFFECTS: Iniencephaly with many related brain and cord defects.

ANIMALS: Rats, F, pregnant (2 strains).

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.25-0.34 mg/kg one dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: End of pregnancy

EXAM. TYPE: Teratology

493>

COMPOUND: Picolinic acid, hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2.2 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

454

COMPOUND: 2-Picolinium, 1-((4-amino-2-propyl-5-pyrimidinyl)methyl)-, chloride, hydrochloride

REFERENCE: Morgan, K.T.
J. Path. 112:229-236, 1974.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, convulsions; cerebrocortical malacia with edema of astrocytes, neuronal degeneration; disruption of meylin sheaths in white-matter

ANIMALS: 21 Lambs, Suffolk x Dorset, M and F, aged 24 hr: 12 treated, 9 controls.

PREPARATION AND DOSE or HISTORY OF PATIENT: 280 mg/kg/d

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 given thiamine 1 mg/d, 5 untreated.

DURATION OF EXPERIMENT: Serial sacr 2-36 hr after neurotoxic signs.

EXAM. TYPE: Behavior, pathology, histology

COMPOUND: 2-Picolinium, 1-((4-amino-2-propyl-5-pyrimidinyl)methyl)-, chloride, hydrochloride

REFERENCE: Morgan, K.T., Coop, R.L. and Doxey, D.L.
J. Path. 116:73-81, 1975.

OBSERVED NEUROTOXIC EFFECTS: Encephalopathy preceded by reduced cerebrocortical transketolase activity.

ANIMALS: 24 Sheep: Suffolk x Dorset lambs aged 24 hr, M and F

PREPARATION AND DOSE or HISTORY OF PATIENT: 280 mg/kg/d in aqueous soln.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 12 matched untreated controls.

DURATION OF EXPERIMENT: Sacr at 7, 14, 21 d.

EXAM. TYPE: Histology, biochemistry

COMPOUND: Picrotoxin

000124878

REFERENCE: Hill, R.G. and Miller, A.A.
Br. J. Pharmac. 50: 425-427, 1974.

OBSERVED NEUROTOXIC EFFECTS: The compound reduced presynaptic inhibition produced by peripheral stimulation, and is a known convulsant. The authors infer that both folic acid and picrotoxin act by the same mechanism.

ANIMALS: 6 piebald Lister rats, adult, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Concentrations: 0.2% w/v (about 3mM)

ROUTE AND SITE: Cannulated onto the surface of the cuneate nucleus

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: About 2 hr per test

EXAM. TYPE: Electrophysiology

495

COMPOUND: Picrotoxin

000124878

REFERENCE: Hill, R.G., Simmonds, M.A. and Straughan, D.W.
Br. J. Pharmac. 45: 176P-177P, 1972 (Abstract of proceedings)

OBSERVED NEUROTOXIC EFFECTS: The convulsive threshold was reached in 20 min; abnormal electrographs were seen before GABA antagonism, and were related with seizures. GABA was ineffective in preventing convulsions.

ANIMALS: Cats, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.15 mg

ROUTE AND SITE: I.V. infusion

CONTROL INFORMATION: Leptazol (6 mg) used as control

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry, behavior

COMPOUND: Picrotoxin

000124878

REFERENCE: Johnston, G.A.R. and Mitchell, J.F.
J. Neurochem. 18:2441-2446, 1971.

OBSERVED NEUROTOXIC EFFECTS: All four compounds influenced the release of GABA, but not its uptake. Biculline, at 10^{-5} M (not more or less) potentiated evoked release of GABA but not the resting release. Metrazol inhibited the electrically resting release but not the electrically evoked release. Strychnine and picrotoxin inhibited the electrically evoked release of GABA.

ANIMALS: In vitro slices of rat cerebral cortex

PREPARATION AND DOSE or HISTORY OF PATIENT: Preincubated with compounds for 15 min, then with labeled GABA for 10 min.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: 25 min

EXAM. TYPE: Biochemistry

COMPOUND: Piperazine

000110850

REFERENCE: Sturman, G.
Br. J. Pharmac. 50: 153-155, 1974.

OBSERVED NEUROTOXIC EFFECTS: Mice: Pretreatment 1 hour beforehand with piperazine enhanced the acute toxicity of chlorpromazine but not of prochlorperazine. Rats: Pretreatment with piperazine enhanced catatonia from chlorpromazine but not from prochlorperazine. Piperazine did not alter the EEG changes induced by chlorpromazine or prochlorperazine. In sum: piperazine potentiated the central nervous system effects of chlorpromazine but not of prochlorperazine.

ANIMALS: Mice, no details
Rats, F, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: Piperazine: 0, 1, 2.5 or 5 g/kg^{-1} followed after 1 or 24 hr by various doses of chlorpromazine or prochlorperazine

ROUTE AND SITE: Piperazine: S.C.; chlorpromazine and prochlorperazine: I.P.

CONTROL INFORMATION: No piperazine given

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Behavior

COMPOUND: 1-Piperazineethanol, 4-(3-(2-chlorophenothiazin-10-yl)propyl)-

000058399

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: ED_{50} 50 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

69?<

COMPOUND: 1-Piperazineethanol, 4-(3-(2-chlorophenothiazin-10-yl)propyl)-, heptanoate

REFERENCE: Pakkenberg, H. and Fog, R.
Psychopharmacologia (Berl) 40:165-169, 1974.

OBSERVED NEUROTOXIC EFFECTS: No significant effects except in (1) where compound increased labeling of nuclei. Authors refer to related paper where 12 mo. of treatment caused 20% loss of cells in basal ganglia and conclude that treatment must be "relatively prolonged."

ANIMALS: 40 Rats, Wistar, approx. 250 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 3.4 mg/kg in sesame oil, 3 times in 6 wks to 10 rats.
(2) As above, except 5 inj. to 10 rats.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 10 rats treated sesame oil 3 times in 6 wk, sacr 3 d after last inj.
10 rats treated sesame oil 5 times.

DURATION OF EXPERIMENT: (1) 6.5 wk, (2) 10.5 wk.

EXAM. TYPE: Autoradiography

4982

COMPOUND: 2-Piperidineacetic acid, α-phenyl-, methyl ester hydrochloride

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 15 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: Piperidine, 2-chloroethyl-, hydrochloride

REFERENCE: Goldin, A., How, H.A., Landing, B.H., Shapiro, D.M. and Goldberg, B.
J. Pharm. Exp. Ther. 94:249-261, 1958.

OBSERVED NEUROTOXIC EFFECTS: Waltzing syndrome was produced by dialkyl and heterocyclic β-chloroethylamines but not when (a) OH or bromine replaced the β chlorine, (b) a β-phenyl group replaced one of the β hydrogens in the chlorinated chain, or (c) phenyl groups were introduced into the dialkyl carbons. No effect from primary/secondary β-chloroethylamines, related quaternary compounds, or bis-, tris-, or tetrakis-β-chloroethylamines. Piperidine and morpholine analogs and arsenetin produced waltzing. Cerebellar and axial lesions found consistent with behavior.

ANIMALS: Mice, CF1, M, 2-3m, 18-25 g; also CF1 F and C3H M.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-625 mg/kg in saline or (insolubles) 10% acacia, various schedules.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle alone

DURATION OF EXPERIMENT: At least 10 d after treatment.

EXAM. TYPE: Behavior, histology.

COMPOUND: 2-piperidineethanol, alpha, alpha-diphenyl-1-methyl-hydrochloride.

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 150 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

4997

COMPOUND: 1-Piperidine propanol, alpha-cyclohexyl alpha-phenyl-, hydrochloride

000052493

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 5, 10 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

500X

COMPOUND: 1-Piperidine propanol, alpha-cyclopentyl-alpha-phenyl-

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: 3-Piperidinol, 1-methyl-, citrate

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 100 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Plumbane, tetraethyl-
000078002

REFERENCE: Cremer, J.E.
Nature (Lond.) 195: 607-608, 1962.
(with reply by Vardanis, A. and Quastel, J.H., ibid. p. 606).

OBSERVED NEUROTOXIC EFFECTS: The compound produced tremors with intermittent convulsions, different from hindlimb paralysis from triethyl lead, an in-vivo metabolite of tetraethyl lead. Glucose was taken up but not oxidized by brain slices (Cremer). There was normal oxidation by less susceptible hooded rats who survive longer, and oxidation is depressed only by triethyl lead (Vardanis and Quastel).

ANIMALS: Rats, (strain ns), M, 200 g (Cremer)
Rats, hooded, M, bred at McGill (Vardanis & Quastel)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg/d for 3 d (Cremer)
10 mg/kg/d for 6 d (Vardanis & Quastel)

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 3-6 d

EXAM. TYPE: Behavior, biochemistry

501>

COMPOUND: Plumbane, tetraethyl-
000078002

REFERENCE: Miklowitz, W.J. and Yeager, D.W.
Life Sci. 13: 897-905, 1973.

OBSERVED NEUROTOXIC EFFECTS: Acute intoxication in frontal cortex, cerebellum, and hippocampus. All contained approx. 33 mcg lead/g dry wt, with significant losses of copper, iron and zinc. Lead: copper movement ratio was 1:1, lead: iron was 1:2, lead: zinc varied. Convulsions and encephalopathy.

ANIMALS: Rabbits, NZ White, M, 2.5-3.5 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg, one dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Mentioned, not described.

DURATION OF EXPERIMENT: Sacr 18-24 hr.

EXAM. TYPE: Biochemistry

502<

COMPOUND: Plumbane, tetraethyl-
000078002

REFERENCE: Niklowitz, W.J.
Neurology 25:927-934, 1975.

OBSERVED NEUROTOXIC EFFECTS: Hippocampus, frontal and cerebellar cortex were examined for ultrastructural changes. Classic neurofibrillary tangles developed in hydropic degenerating neurons and comprised mainly bundles of smooth tubules 200 A diam. and of "enormous length."

ANIMALS: 16 Rabbits, NZ White, M, 2.5-3.5 kg, quarantined for 2 wk.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg, one dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial Sacr 6-12 hr.

EXAM. TYPE: Histology

COMPOUND: Pregn-4-ene-3,20-dione, 17,21-dihydroxy-, succinate, sodium salt

REFERENCE: Heuser, G., Ling, G.M. and Buchwald, N.A.
Arch. Neurol 13:195-203, 1965.

OBSERVED NEUROTOXIC EFFECTS: (1) Low doses (5 mg/kg) produced slow wave EEG and intermittent sedation. Doses of 20-70 mg/kg resulted in sleep-like behavior. Complete recovery was observed within several hours. Total of 100-200 mg/kg produced seizures, from which 3/4 animals recovered, 1 died. (2) Dose of 40-70 mg/kg resulted in syndrome of alternating periods of sedation and alertness. Acute doses of 200 mg/kg elicited repeated myoclonic jerks, and tonic-clonic seizures were seen after doses of 300 mg/kg or more. (3) Dose of 40-70 mg/kg produced sedation and slow wave activity, 100-150 mg/kg produced tonic seizures and falling spells, 200 mg/kg and greater gave tonic-clonic convulsions.

ANIMALS: Monkeys: (1) Cebus (2) Rhesus (3) Squirrel

PREPARATION AND DOSE
or HISTORY OF PATIENT: Varying doses, approx 5-200 mg/kg.

ROUTE AND SITE: I.V. or I.P.

CONTROL INFORMATION: Sham inj as well as saline and sodium bicaronate soln were used as controls. Control inj did not produce sedative or convulsion effects.

DURATION OF EXPERIMENT: Up to approx 30 min/test

EXAM. TYPE: Electrophysiology, behavior

COMPOUND: Proline, 5-oxo-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

503>

COMPOUND: 1,2-Propanediol, dinitrate
006423434

REFERENCE: Stewart, R.D., Peterson, J.E., Newton, P.E., Hake, C.L., Hosko, M.J., Lebrun, A.J., and Lawton, G.M.
Toxicol. Appl. Pharmacol. 30: 377-395, 1974.

OBSERVED NEUROTOXIC EFFECTS: 0.2ppm or more caused headache and disruption of the visual evoked response. 0.5ppm for 6.5 hours produced impairment in balance.

ANIMALS: Human, 19 M aged 22-51 yr, 1 F aged 24 yr

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.03 to 1.5ppm for 1 to 8 hr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: Subjects prior to exposure

DURATION OF EXPERIMENT: 1 d

EXAM. TYPE: Clinical

504>

COMPOUND: 1,3-Propanediol, 2-methyl-2-propyl-, dicarbamate
000057534

REFERENCE: Meyerowitz, S. and Satran, R.
Neurology 10: 1103-1105, 1960.

OBSERVED NEUROTOXIC EFFECTS: The subject exhibited high-voltage fast activity in his EEG at 28 hr, less at 44 hr, abnormalities at 91 hr, and persistent occasional slow activity at 14 d.

ANIMALS: Human, 1 M, 19

PREPARATION AND DOSE or HISTORY OF PATIENT: Overdose of 160 g

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 14 d

EXAM. TYPE: Clinical, EEG

COMPOUND: 1-Propene-1,1,3-tricarbonitrile, 2-amino-

REFERENCE: Davenport, J.W.
Science 167:1007-1009, 1970.

OBSERVED NEUROTOXIC EFFECTS: Poor performance of closed-field maze tests during and long after treatment. Eight learning tests were not helped by treatment with compound.

ANIMALS: Rats, Holtzman, pregnant F d 5 gestation.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 1.5 g/kg diet.
(2) 1.0 g/kg diet.
Diets fed during gestation and lactation, and to offspring after weaning until ages 130 or 212 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: (1) Control rats with plain mash diet.
(2) 2 grps: plain diet or diet with 1.0 g thiouracil/kg diet.

DURATION OF EXPERIMENT: Until offspring were (1) 130 d -or- (2) 212 d old.

EXAM. TYPE: Behavior

COMPOUND: Propionic acid, 2-amino-3-hydroxy-, phosphonate, (ester)

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: The compound was toxic to non-neurol components (glia, etc.), but not to neurons.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

505>

COMPOUND: Propionic acid, 2-amino-3-sulfino-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

506

COMPOUND: Propionic acid, beta-N-oxalyl-L-alpha, beta-diamino (Lathyrus sativus neurotoxin)

REFERENCE: Cheema, P.S., Padmanaban, G. and Sarma, P.S.
J. Neurochem. 18:2137-2144, 1971.

OBSERVED NEUROTOXIC EFFECTS: Lathyrism involves tremors and convulsions. Increases of brain adenylic acid deaminase, glutaminase, transglutaminase, acid protease, aspartate-α-ketoglutarate transaminase, and aspartate-pyruvate transaminase were found; glutamate dehydrogenase was diminished slightly; glutamine synthetase was unchanged. Authors concluded that ODAP-induced protein degradation might have liberated excess ammonia.

ANIMALS: Rats (breed ns.), aged 12 d, 15-20 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 1.4 mmol/kg in saline

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicle only

DURATION OF EXPERIMENT: 7 or 60 min after treatment

EXAM. TYPE: Biochemistry

COMPOUND: Propionic acid, beta-N-oxalyl-L-alpha, beta-diamino-

REFERENCE: Rao, S.L.N. and Sarma, P.S.
Biochem. Pharm. 16: 218-220, 1967.

OBSERVED NEUROTOXIC EFFECTS: Ataxia and paralysis

ANIMALS: Cockerels, adult, 650-750 g
Rats, Adult, 100-120 g
Mice, adult, 30-35 g
A monkey, M, 1.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Prepared cockerels, 100 mg of compound (controls aspartic acid)
Rats and mice: 500 mg/kg
Monkey: 200 mg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Yes, but no details

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, biochemistry

COMPOUND: Propionitrile, 3-diamino-

REFERENCE: Hartmann, H.A. and Stitch, H.F.
Science 125:445, 1975.

OBSERVED NEUROTOXIC EFFECTS: Hyperactivity and abnormal movements in rats for next 5 mo., mice became "waltzing"; birds hyperactive and moved abnormally; fish brief hyperactivity and abnormal posture, reevokable later; grasshoppers leapt further and tetrahymena migrated faster than normal.

ANIMALS: Rats: S-D - 200 g, Long-Evans - 280 g. Grasshoppers (Melanopus
Mice: Albino Protozoan (Tetrahymena)
Birds: (Melopsittacus undulatus)
Fish: (Lepomus gibbosus)

PREPARATION AND DOSE
or HISTORY OF PATIENT: Rats 0.1-10 g/kg one dose; mice 1.5-2 g/kg one dose; Birds 2 g/kg; fish 2 g/kg; grasshoppers 1-2 g/kg; Tetrahymena 0.01% in medium.

ROUTE AND SITE: Rats, mice, birds: I.P. Fish and grasshoppers: intraabdominal

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

5072

COMPOUND: Propionitrile, 3,3'-iminodi-

000111944

REFERENCE: Chou, S-M. and Hartmann, H.A.
Acta Neuropath. 3: 428-450, 1964.

OBSERVED NEUROTOXIC EFFECTS: No deaths; waltzing syndrome and body weight loss within 48 hr of last dose, many symptoms persisted for 1 yr. Affected nerves: brain-stem least myelinated large neuron axons in reticular system, VIIIth nerve nuclei, cord anterior horns, cranial nerves, especially neurons in which enzyme transport depends on axonal flow. Good correlation between behavior and histology.

ANIMALS: 40 rats, S-D, M, 200 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2 g/kg (in one dose or in 4 doses at 3-d intervals) in buffer

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Mentioned, not described

DURATION OF EXPERIMENT: Serial sacr 2 d to 6 mo (1 yr observation of some)

EXAM. TYPE: Behavior, histology

508A

COMPOUND: Propionitrile, 3,3'-iminodi-

000111944

REFERENCE: Chou, S-M and Hartmann, H.A.
Acta Neuropath. 4:590-603, 1965.

OBSERVED NEUROTOXIC EFFECTS: All developed waltzing syndrome. Electron-microscopical description of axonal balloon lesions: edema and degeneration.

ANIMALS: 5 Rats, S-D, M, 100-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5 g/kg every 3 d for 6 doses.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr 6-11 wk.

EXAM. TYPE: Behavior, histology

COMPOUND: Propionitrile, 3,3'-iminodi-

REFERENCE: Hartmann, H.A., Lalich, J.J. and Akert, K.
J. Neuropath. Exp. Neurol. 17:298-304, 1958.

OBSERVED NEUROTOXIC EFFECTS: After 3-4 wk characteristic jerking and rotational movements of heads. After 8 wk ataxia and paresis of the hind-limb. Degeneration of intraspinal axons of the anterior motor horn cells.

ANIMALS: 12 Rats, S-D, 75 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mg/rat/d in diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: 12 rats unttd.

DURATION OF EXPERIMENT: Serial sacr 9, 12, 15 wk

EXAM. TYPE: Behavior, histology

COMPOUND: Propionitrile, 3,3'-iminodi-

000111944

REFERENCE: Slagel, D.E. and Hartmann, H.A.
J. Neuropath. Exp. Neurol. 24(4): 599-620, 1965.

OBSERVED NEUROTOXIC EFFECTS: Extensor hypertonus of neck and forelimb, retropulsion, choreoathetotic head movements, rapid circling. Axonal swelling in brain and cord; lateral and medial vestibular nuclei, caudal pontine reticular nucleus, ventral horn (lumbar, thoracic and cervical); spinal, accessory, hypoglossal, vagus, parafacial, abducens, motor Vth, mesencephalic Vth, trochlear, and oculomotor nuclei. Neurology and behavior were correlated.

ANIMALS: (1) 7 mice, Swiss Webster, (2) 14 mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.2 g/ml in 0.9% saline pH 7.0 (HCl), 2-3 g/kg, 4-9 doses.

ROUTE AND SITE: Injections

CONTROL INFORMATION: 7 controls, saline only; (2) 10 mice

DURATION OF EXPERIMENT: 4-10 wk

EXAM. TYPE: Behavior; histology

509

COMPOUND: Propionitrile, 3,3'-iminodi-

000111944

REFERENCE: Tews, J.K., Kopf, G.M. and Stone W.E.
Int. J. Neuropharmacol. 7: 29-34, 1968.

OBSERVED NEUROTOXIC EFFECTS: (1) Brains analysed for 30 (total) free amino acids and other compounds showed only (a) low valine, and (b) a tendency toward increased phosphorylation of nucleosides (more triphosphates, less diphosphates).
(2) and (3) Cats and dogs showed no hyperactivity but ataxia, depression, anorexia and retropulsion. EEG changes in cats were not related to clinical symptoms.

ANIMALS: (1) Mice, Rolfsmeyer, F, 7-8 wk old
(2) Cats, surgically prepared
(3) Three Dogs

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Hyperactivity doses of 3 g/kg and up
(2) Mostly single doses 200-400 mg/kg
(3) 100-300 mg/kg

ROUTE AND SITE: (1) S.C.; (2) I.P.; (3) ns

CONTROL INFORMATION: (1) Untreated (2, 3) ns

DURATION OF EXPERIMENT: 7-11 d

EXAM. TYPE: (1) Biochemistry; (2) EEG; (3) Behavior

510

COMPOUND: Propionitrile, 3,3'-iminodi-

000111944

REFERENCE: Vivanco, F., Busturia, M.A., Ramos, F. and Sanchez-Martin, J.A. J. Neurochem. 19:563-565, 1972.

OBSERVED NEUROTOXIC EFFECTS: Cyanoacetic acid (metabolite of compound) in plasma and brain of poisoned rats lower than in thyroxine-protected rats. Thyroxine rats excreted more metabolite in urine.

ANIMALS: 27 Rats, M, 100-150 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 60 mg/rat/d, for 2 d (15 rats)

ROUTE AND SITE: S.C.

CONTROL INFORMATION: 12 rats pretreated with 0.2 mg/d Na-L-thyroxinate for 5 d

DURATION OF EXPERIMENT: 3 d (1 d after last dose of compound)

EXAM. TYPE: Biochemistry

COMPOUND: Propyl alcohol (Propanol)

000071238

REFERENCE: Roach, M.K., Davis, D.L., Pennington, W. and Nordyke, E. Life Sci. 12(1):433-441, 1973.

OBSERVED NEUROTOXIC EFFECTS: Propanol inhibited active transport of probable neurotransmitters of the central nervous system by synaptosomes. Authors conclude that alcohol interacts with membrane lipids of synaptosome.

ANIMALS: Rats, S-D, M, 200-250 g, brains removed and homogenates incubated in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: Propanol added as 25% soln, at start of preincubation period. Propanol conc 5-30 mg/ml. Incubated in vitro with labeled norepinephrine, GABA and glutamate.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Control: incubation in medium with no alcohol.

DURATION OF EXPERIMENT: Laboratory procedure.

EXAM. TYPE: Biochemistry

COMPOUND: Propylamine

000107108

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Ranshaw cells or dorsal horn interneurones in lumber cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

511

COMPOUND: Pseudomona tabaci exotoxin

REFERENCE: Sinden, S.L. Durbin, R.D., and Uchytil, T.F.
Toxic. Appl. Pharmac. 14: 82-88, 1969.

OBSERVED NEUROTOXIC EFFECTS: (1) Severe convulsions with minimal dose of 0.025 mmole/kg I.P.; became uncoordinated; and then spastic.
(2) Severe convulsions with minimal dose .0003 mmoles/kg in rats intracisternally.

ANIMALS: (1) Mice, weanling SW, 10g
(2) Rats, Holtzman, 135g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5 ml toxin soln (methanol extracts of concentrated culture filtrate 3% pure by weight) and doses of 0.0125-0.3 mmoles/kg I.P. ; 0.00015-0.0006 mmoles/kg intracisternally. Doses were heated.

ROUTE AND SITE: I.P. and intracisternally

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: .1-12 hrs I.P.; 10-20 mins intracisternally

EXAM. TYPE: Behavior

512

COMPOUND: 3-Pyridenecarboxamide, 6-amino-

000329895

REFERENCE: Chamberlain, J.G.
Teratology 3:377-388, 1970.

OBSERVED NEUROTOXIC EFFECTS: Central nervous system and growth retardation at 24 hr, with fluid movement into ventricles. Normal pressure by d 21, and evidence of early hemorrhage nearly gone.

ANIMALS: Rats, Long-Evans, F, av 100 d old, 225 g, bred with males.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 8 mg/kg on d 13, single dose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls fasted or given sterile H_2O, i.p.

DURATION OF EXPERIMENT: Serial sacr .25 to 8 d after dose.

EXAM. TYPE: Histology, biochemistry

COMPOUND: 3-Pyridenecarboxamide, 6-amino-

000329895

REFERENCE: Turbow, M.M., Clark, W.H., and DiPaolo, J.A.
Teratology 4:427-432, 1971.

OBSERVED NEUROTOXIC EFFECTS: Multiple defects: exencephaly, anophthalmia and hydrocephalus. Day 8 and 9 embryos responded to 5 mcg, day 7 embryos needed 50-100 mcg.

ANIMALS: Hamsters, F, 8-12 wk age

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 5-100 mcg in 5 or 10 mcl water to 1/2 or 1/3 of implantation sites once during d 7-9 of pregnancy; remaining sites given one of 3 control treatments.
(2) 8 mg/kg once during d 7-9 of pregnancy.

ROUTE AND SITE: (1) Intraamniotic inj.
(2) I.P.

CONTROL INFORMATION: Implanted embryos given 5 mcl water, needle-puncture only, or no treatment. In one group all implantations were so treated.

DURATION OF EXPERIMENT: 14 d.

EXAM. TYPE: Teratological

COMPOUND: 3-Pyridenecarboxamide, 6-amino-

000329895

REFERENCE: Chamberlain, J.G. and Nelson, M.M.
Teratology 3(4):285-292, 1970.

OBSERVED NEUROTOXIC EFFECTS: Cellular changes in fetal brains 24 hr after dose. Hydrocephalus frequent. Prevented by equal injections of nicotinamide.

ANIMALS: Rats, Long-Evans, F, age 100 d, 225 g, bred. One group treated d 9-20 of pregnancy.

PREPARATION AND DOSE or HISTORY OF PATIENT: 8 mg/kg, 1 dose in water.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 14 rats received water, i.p.

DURATION OF EXPERIMENT: 21 d

EXAM. TYPE: Teratological

513<

COMPOUND: 3-Pyridenecarboxamide, 6-amino-

000329895

REFERENCE: Wolf, A. and Cowen, D.
Bull. N.Y. Acad. Med. 35:814-816, 1959.

OBSERVED NEUROTOXIC EFFECTS: Progressive limb weakness starting in hindlimbs and extending to other muscles, speed of onset dose-related, no convulsions; grey-matter of cord (not white-matter or PNS), focal lesions of geniculate bodies, thalamus and corpus striatum; degeneration of axons and myelin (rats). Additional degeneration of brain cortex and sciatic nerve (cats). Similar lesions to rats (dogs).

ANIMALS: 16 rats, 4 cats, 2 dogs, and additional rats.

PREPARATION AND DOSE or HISTORY OF PATIENT: 8 mg/kg (16 rats), 16-64 mg/kg (additional rats), 30 mg/kg (cats) - all single doses. 4 mg/kg "repeatedly" (dogs)

ROUTE AND SITE: I.P. (rats), I.V. or I.P. (cats), I.V. (dogs)

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Serial sacr to 10 d (rats and dogs) or 20 d (cats)

EXAM. TYPE: Behavior, histology

514

COMPOUND: Pyridine, 2-((2-(dimethylamino)ethyl)(p-methoxybenzyl)amino)-, maleate (1:1)

REFERENCE: Quinton R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} >50 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: 3-Pyridinemethanol, 5-hydroxy-4,6-dimethyl-, hydrochloride (4-Deoxypyridoxine HCL

000148516

REFERENCE: Horton, R.W. and Meldrum, B.S.
Br. J. Pharmac. 49: 52-63, 1973.

OBSERVED NEUROTOXIC EFFECTS: Seizures, photic stimulation, EEG changes, inhibition of brain glutamate carboxylase were caused by 3-mercaptopropionic acid more strongly than by allylglycine or 4-deoxypyridoxine HCl. Thus the authors concluded that seizures were due to depletion of glycine and γ-aminobutyric acid (GABA).

ANIMALS: Mice, CFW or BALB/C, M, 20-30 g
10 Baboons (Papio papio), adolescent, from Senegal, 3-6 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: ED_{50} and latency 1.1 mmole/kg, 42.3 min.
Baboons: ED_{50} and latency 0.53 mmol/kg, 46 min.

ROUTE AND SITE: Mice I.P., Baboons I.V.

CONTROL INFORMATION: Timed studies

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Mice: behavior, biochemistry; baboons: polygraph.

COMPOUND: Pyridinium, 2-formyl-1-methyl-, chloride, oxime

REFERENCE: Crook, J.W., Cresthull, P., O'Neil, H.W. and Oberst, F.W. Tox. Appl. Pharm. 6: 310-315, 1964.

OBSERVED NEUROTOXIC EFFECTS: Occasional ataxia, collapse, tremors in dogs, no changes in red-cell cholinesterase, no signs in rabbits, no pathology by photomicroscopy.

ANIMALS: 3 mongrel dogs, 7-11 kg
5 white rabbits, ca. 2.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Dogs: 25 mg/kg twice daily, 5 d/w for 6 w
Rabbits: 50 mg/kg/d, 5d/w for 6 w

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 wk

EXAM. TYPE: Behavior, blood tests, autopsy

515

COMPOUND: Pyridinium, 2-formyl-1-methyl-, methanesulfonate, oxime

REFERENCE: Crook, J.W., Cresthull, P., O'Neil, H.W. and Oberst, F.W. Tox. Appl. Pharm. 6:310-315, 1964.

OBSERVED NEUROTOXIC EFFECTS: Occasional ataxia, collapse, tremors in dogs, no changes in red-cell cholinesterase, no signs in rabbits, no pathology by photomicroscopy.

ANIMALS: 3 mongrel dogs, 7-11 kg
5 white rabbits, ca. 2.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Dogs: 25 mg/kg twice daily, 5 d/w for 6 w
Rabbits: 50 mg/kg/d, 5d/w for 6w

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 wk

EXAM. TYPE: Behavior, blood tests, autopsy

516

COMPOUND: (3H-Pyrido-(3,4-b)indole, 4,9-dihydro-7-methoxy-1-methyl-
000304212

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: 9H-Pyrido(3,4-b)indole,-7-methoxy-1-methyl-
000442513

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: 9H-Pyrido(3,4-b) indole, 7-methoxy-1-methyl-, hydrochloride

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced excitement, abnormal postures, arousal EEGs, then depression.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 10-50 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

517

COMPOUND: 9H-Pyrido(3,4-b)indole, 1,2,3,4-tetrahydro-7-methoxy-1-methyl

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

518

COMPOUND: 9H-Pyrido(3,4-b)indole, 1,2,3,4-tetrahydro-2-methyl-

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: 9H-Pyrido(3,4-b)indol-7-ol, 1-methyl-

REFERENCE: Rivier, L. and Lindgren, J-E.
Econ. Bot. 26: 101-129, 1972.

OBSERVED NEUROTOXIC EFFECTS: Hallucinatory (visual)

ANIMALS: Humans: anecdotal and personal experiences

PREPARATION AND DOSE or HISTORY OF PATIENT: Identification and quantitation analyses, still not complete as reported, indicate that 200 ml of drink (normal dose) includes 30 mg harmine, 10 mg TH-harmine and 25 mg DMT (relative amounts in separate ingredients found to be different), taken up to 10 times/mo or more.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Expedition, duration ns

EXAM. TYPE: Behavior, analytical chemistry

COMPOUND: Pyridoxol hydrochloride

REFERENCE: Alder, S. and Zbinden, G.
Agents and Actions 3/4: 233-243, 1973.

OBSERVED NEUROTOXIC EFFECTS: Irritability after 1 wk on 2 x 500 mg/kg. Hot Plate Test positive after 8-18 d and on day 25 (500 mg level); Foot Print Test ns, but Rotating Rod Test was failed by rats on 500 mg level. Sciatic nerve degeneration seen after 10 x 500 mg doses, no changes in brain and cord, moderate effects on bone-marrow.

ANIMALS: Rats, CFN Zu, F, 38-53g, 6 groups 10-12 each

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100, 250, 500 mg/kg, 5d/wk, 2 groups/level, 5-40 doses

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 2 groups saline I.P.

DURATION OF EXPERIMENT: Serial sacr 1-8 wk

EXAM. TYPE: Behavior, histology

519

COMPOUND: Pyridoxol, methoxy-

REFERENCE: Purpura, D.P. and Gonzalez-Montesgudo, O.
J. Neuropath. Exp. Neurol. 19(3):421-432, 1960.

OBSERVED NEUROTOXIC EFFECTS: Generalized seizures in 30-45 min, monitored by EEG recorded epidurally from neocortex. Hippocampal pyramidal neurons damaged within 2 hr (shrunken with loss of internal structure). In Ammon's horn CA_3-CA_1(endblade) neurons altered selectively. Same sort of changes also seen at 6 hr after dose.

ANIMALS: 51 Cats, adult, 2.4 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 18 cats given 50 mg/kg.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: 32 controls given various treatments.

DURATION OF EXPERIMENT: Observation 2-6 hr after dose, then sacr.

EXAM. TYPE: Behavior; histology.

520

COMPOUND: 4-Pyrimidinecarboxylic acid. 1,2,3,6-tetrahydro-2,6-dioxo-5-fluoro-

REFERENCE: Koenig, H.
Science 127:1238-1239, 1958.

OBSERVED NEUROTOXIC EFFECTS: Severe ataxia of trunk and extremities, fatal in some. Not seen in "control studies". Advanced chromatolysis of Purkinje cells of cerebellum.

ANIMALS: Cats

PREPARATION AND DOSE or HISTORY OF PATIENT: 3-10 mg, one dose, in some cases repeated to make total of 5-15 mg (per cat).

ROUTE AND SITE: Intracisternal

CONTROL INFORMATION: Not described, except that orotic acid and i.p. injections were mentioned as "control studies".

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, histology (incomplete at time of writing).

COMPOUND: 4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-5-fluoro-

REFERENCE: Kury, G. and Craig, J.M.
Arch. Path. 81: 166-173, 1966,

OBSERVED NEUROTOXIC EFFECTS: Exencephaly with severe brain malformations, neuraxis with necrotic neuroblasts. Microphthalmia and necrotic neurons in neuraxis.

ANIMALS: Eggs, White Leghorn, fertilized

PREPARATION AND DOSE or HISTORY OF PATIENT: Teratogenic dosage schedules, from d 1 to d 4

ROUTE AND SITE: Inoculation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 21 d

EXAM. TYPE: Teratological

COMPOUND: 4,6(1H,5H)-Pyrimidinedione, 5-ethyldihydro-5-phenyl- (Primidone)

000125337

REFERENCE: Brillman, J., Gallagher, B.B. and Mattson, R.H.
Arch. Neurol. 30:255-258, 1974.

OBSERVED NEUROTOXIC EFFECTS: Central Nervous System depression and disequilibrium, due "mostly" to primidone itself, rather than its metabolites phenobarbital and/or phenylethylmalonamide.

ANIMALS: 2 Human cases of overdose, 1M age 51 an epileptic, 1 F age 18.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Male: estimated intake 5 g; Female: 22.5 g in 12 hr. Commercial preparation.

ROUTE AND SITE: Oral

CONTROL INFORMATION:

DURATION OF EXPERIMENT: Male 23 d, Female 7 d.

EXAM. TYPE: Behavior, clinical laboratory

521<

COMPOUND: Pyrocatechol, 4-(2-aminoethyl)-5-hydroxy-

REFERENCE: Sachs, C. and Jonsson, G.
Res. Comm. Chem. Path. Pharm. 4: 203-220, 1972.

OBSERVED NEUROTOXIC EFFECTS: Compound produced a permanent, though incomplete, chemical sympathectomy. The compound penetrated the blood-brain barrier in newborn animals and depressed norepinephrine uptake by selected nerves. Cortex and cord neurons were more susceptible than those in the hypothalamus.

ANIMALS: Rats, S-D, newborn
Mice, N.M.R.I., newborn

PREPARATION AND DOSE
or HISTORY OF PATIENT: 100 mg/kg in sodium chloride
0.05 ml per rat or mouse within 4 hr of birth and at 24-hr intervals for 3 doses

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Matched controls

DURATION OF EXPERIMENT: 10-14 wk

EXAM. TYPE: Biochemistry

522

COMPOUND: Pyrocatechol, 4-(2-aminoethyl)-5-hydroxy-

REFERENCE: Simon, H., LeMoal, M., Galey, D. and Cardo, B.
Exp. Brain Res. 20: 375-384, 1974.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused terminal degeneration in nucleus caudatus-putamen or nucleus accumbens, depending on injection site.

ANIMALS: 9 rats, S-D, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.5 and 1 mcg

ROUTE AND SITE: Injection into ventral mesencephalic tegmentum

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 3d

EXAM. TYPE: Histology

COMPOUND: Pyrocatechol, 4-(2-aminoethyl)-5-hydroxy-

REFERENCE: Votavova, M., Boullin, D.J. and Costa, E.
Life Sci. 10(1):87-91, 1971.

OBSERVED NEUROTOXIC EFFECTS: Noradrenaline depleted in peripheral neurons, 5-HT not affected. Author's conclude failure to affect 5-HT indicates that indolylalkylamine is definitely not present in sympathetic nerves.

ANIMALS: Cats, F, 2.5-4.5 kg.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20 mg/kg, in 0.5 ml soln containing 6 mg/ml ascorbic acid, followed after 14 d with 50 mg/kg. 200,000 I.U. of procaine penicillin, i.m., followed each inj.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: 5 cats inj with ascorbic acid.

DURATION OF EXPERIMENT: 21 d

EXAM. TYPE: Biochemistry

COMPOUND: Pyrophosphoric acid, tetraethyl ester
000107493

REFERENCE: Rayner, M.D., Popper, J.S., Carvalho, E.W. and Hurov, R.
Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE: Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

523

COMPOUND: Pyrrole, 2,4-dimethyl-3-ethyl-

REFERENCE: Walker, J.L.
Pharmac. Biochem. Behav. 3: 243-250, 1975.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused ataxia, hyperventilation, locomotor depression and catalepsy. EEG tests showed low frequency hypersynchronous changes intermittent with acute asynchronous spiking activity. The author concluded that the compound caused major central nervous system dysfunction on the lines of drug-induced psychoses.

ANIMALS: Rats, hooded, 311-465 g, total 10, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 10-90 mcl/kg (9.1-82 mg/kg) per d for up to 8 d

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Pre-drug data

DURATION OF EXPERIMENT: Up to 8 d

EXAM. TYPE: Behavior, EEG, histology

524

COMPOUND: 3-Pyrrolidine acetic acid, 2-carboxy-4-isopropenyl

REFERENCE: Olney, J.W., Rhee, V. and Ho, O.L.
Brain Res. 77:507-512, 1974.

OBSERVED NEUROTOXIC EFFECTS: Convulsions: infants from 15 min, some at 1 mg/kg s.c., all at 5 mg/kg or more, and orally, some at 3 mg/kg, all at 7 mg/kg or more. Adults s.c., none at 20 mg/kg, all at 40 mg/kg; orally, some at 40 mg/kg, and 60% at 100 mg/kg. Lesions in arcuate nucleus of hypothalamus, some in hippocampus; none in controls.

ANIMALS: 16 litters of mice aged 7 d; 126 adult mice aged 6-8 wk.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1-10 mg/kg (infants), 10-100 mg/kg (adults), 6 animals/dose and /route, 1 dose/animal.

ROUTE AND SITE: Gavage or s.c.

CONTROL INFORMATION: 6 Infants, 6 adults, NaCl

DURATION OF EXPERIMENT: 1-3 hr.

EXAM. TYPE: Behavior, histology

COMPOUND: Pyrrolidine, 1,1-(2-butynylene) di-

000051730

REFERENCE: Brumlik, J. and Means, E.D.
Brain 92:157-190, 1969.

OBSERVED NEUROTOXIC EFFECTS: Tremors compared in detail with those of virus-induced acute cerebellar ataxia in man and with parkinsonism.

ANIMALS: Dogs, F, adult, 3

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, electrophsiology

COMPOUND: Pyrrolidine, 1,1 -(2-butynylene)di-

000051730

REFERENCE: McColl, J.D. and Rice, W.B.
Tox. Appl. Pharm. 4:263-268, 1962.

OBSERVED NEUROTOXIC EFFECTS: ED_{50} for producing tremors was 5.8 (4.7-7.1) mg/kg.

ANIMALS: Mice, CFW, 20 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: Graded doses

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Untrtd, trtd with antagonists

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

525A

COMPOUND: 1-Pyrrolidine propanol, alpha-cyclohexyl-alpha-phenyl-

000077372

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 15 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

526

COMPOUND: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-
000072446

REFERENCE: Geldmacher-Mallinckrodt, M. and Lautenbach, L.
Arch. Toxikol. 20:31-37, 1963.

OBSERVED NEUROTOXIC EFFECTS: Case 1 died after 40 hr, case 2 made a slow recovery, case 3 recovered in 48 hr. Clonic convulsions noted.

ANIMALS: Humans: 3 cases of overdoses.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) M, 25, took 20 tablets, total 8 g; (2) M, 26 took 60 tablets; (3) F, 24, took 20 tablets.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical

COMPOUND: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-
000072446

REFERENCE: Marks, P.
Practitioner 212: 721-722, 1974.

OBSERVED NEUROTOXIC EFFECTS: The subject experienced "glove" paresthesia and weakness of hands and loss of tendon reflexes from immediately after the first dose. Tendon reflexes returned in 24 hr after cessation of intake, sensations in 24 hr, power in 36 hr, and paresthesias disappeared after 48 hr. Conclusion: bilateral symmetrical peripheral neuropathy of mixed type, reversible.

ANIMALS: Human: one case, M, 50

PREPARATION AND DOSE or HISTORY OF PATIENT: History noncontributory. 250 mg/night for sleeping. 4 nights.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 d

EXAM. TYPE: Clinical

COMPOUND: Quinine, monohydrochloride
000130892

REFERENCE: Hoffmann, F.A.
Archiv. Exp. Path. Pharm. (Berlin) 17: 363-366, 1883.

OBSERVED NEUROTOXIC EFFECTS: The injections produced convulsions, which the author attributed to a central nervous system reaction.

ANIMALS: Humans: used to reduce pyrexia of typhus, 2 cases of adverse reactions

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.8 grains; 2 doses of 40 and 60 grains

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

S27<

COMPOUND: Quinolines, 8-amino- (not specified)

REFERENCE: Udall, V.
Proc. Roy. Soc. Med. 65: 197-199, 1972.

OBSERVED NEUROTOXIC EFFECTS: Functional blindness, no retinal damage, extensive brain damage including lateral geniculate nucleus.

ANIMALS: Monkeys, rhesus or cynomolgus

PREPARATION AND DOSE
or HISTORY OF PATIENT: ns, used against malaria

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Histology

528

COMPOUND: Quinoline, 7-chloro-4-(4-diethylamino-1-methyl-butylamino)-diphosphate

000050635

REFERENCE: Klinghardt, G.W.
Acta Neuropath. 28: 117-141, 1974

OBSERVED NEUROTOXIC EFFECTS: "Neuronal storage dystrophy:" mainly in posterior root and trigeminal ganglia. Some differences between rats and rabbits. Axonal dystrophy in central nervous system. Myelin breakdown in peripheral nervous system. Considered due to phospholipidosis.

ANIMALS: (1) Rats, Wistar-Stamm, 100-200 g or 40-50 g
(2) 14 Rabbits, 0.9-1.4 kg

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) 250, 375 mg/kg/d, estimated uptake 200 mg/kg/d
(2) 100-165 mg/kg/d

ROUTE AND SITE: Gavage

CONTROL INFORMATION: None found (full translation not performed)

DURATION OF EXPERIMENT: 47-290 d (rats); 138 d (rabbits).

EXAM. TYPE: Histology, histochemistry

COMPOUND: Quinoline, 7-chloro-4((4-(diethyl amino)-1-methylbutyl)amino)-

00054057

REFERENCE: Tiechner, K.H.
Acta Neuropath. 22:208-221, 1972.

OBSERVED NEUROTOXIC EFFECTS: Perikarya contained many multilamellated bodies; also found in Schwann cells, fibroblasts and axons; myelin lamellae were split and degenerated; in 10% of neurons nuclei had 2 types of granular inclusions and the nucleoli could not be found but nucleolar satellites persisted (claimed as a new finding).

ANIMALS: Dorsal root ganglia from Wistar fetal rat in culture.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2×10^{-4} M in media for 6-21 d

ROUTE AND SITE: In vitro.

CONTROL INFORMATION: Laboratory controls

DURATION OF EXPERIMENT: 6-21 d

EXAM. TYPE: Microscopy

COMPOUND: Quinoline, 8-((4-diethylamino)-1-methylbutyl) amino)-6-methoxy-

REFERENCE: D'Agostino, A.N.
Neurology 14: 114-124, 1964.

OBSERVED NEUROTOXIC EFFECTS: Focal degeneration of (a) neurons, with loss of Nissl substance, mitochondrial edema and (Schwann cells) cytoplasmic inclusions, and (b) axons, resembling wallerian degeneration.

ANIMALS: 8 albino rats, adult

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg initially; then 20 mg/kg at 6 h intervals

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Yes, but no details, except saline dose.

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Histology

529

COMPOUND: Quinoline, 6-methoxy-8-(3-diethylaminopropylamino)-

REFERENCE: Schmidt, I.G. and Schmidt, L.H.
J. Neuropath. Exp. Neurol. 7:368-398, 1948

OBSERVED NEUROTOXIC EFFECTS: Selective degeneration in the central nervous system: acute - in proprioceptive pathways; subacute - damage more selective. At 1/2 MTD lesions limited to cord and brainstem (proprioceptive nuclei). Chronic low-dose exposures and long recovery showed massed microglia, astrocytes and neuroglia in injured areas.

ANIMALS: 22 Rhesus monkeys (Macaca mulatta)

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.125 to 6.0 mg base/kg, every 8 hr., in soln as hydroiodide salt.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Acute: 6 hr, chronic: 22d

EXAM. TYPE: Histology

530

COMPOUND: 8-Quinolinol
000148243

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 48 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinol, 5-chloro-3'-hydroxy-2'-naphthoate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 215 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinol, 5-chloro-3'-hydroxy-2'-napthalate, copper (II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and conper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE
or HISTORY OF PATIENT: LD_{50}: 39 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

531<

COMPOUND: 8 Quinolinol,5-chloro-7-iodo-
000130267

REFERENCE: Castaigne, P., Rondot, P., Lenoel, Y., Ribadeau Dumas, J.-L., and Autret,
Therapie 28:393-400, 1973.

OBSERVED NEUROTOXIC EFFECTS: Paraplegia, sphincter disturbance, withdrawal reflexes, peripheral amyotrophy, optic neuritis. No change during 4 mo. of observation in hospital. Syndrome labeled subacute myelo-optico-neuritis.

ANIMALS: 1 Human, F, aged 55 yr.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1500 mg/d for 1 mo. as Enterovioform.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 4 mo.

EXAM. TYPE: Clinical and biochemistry

5C2A

COMPOUND: 8 quinolinol,5-Chloro-7-iodo-
000130267

REFERENCE: Ferrier, T.M. and Eadie, M.J.
Med. J. Aust. 2: 1008-1009, 1973.

OBSERVED NEUROTOXIC EFFECTS: The compound produced sudden severe failure of recent memory, with headache and confusion. The EEG remained normal and recovery began on the third day, but a memory gap persisted throughout the study. The author comments on permanent losses and hippocampal damage in animals.

ANIMALS: Human: F, 43 and M, 32

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1500 mg; 2 g

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: To 1 mo

EXAM. TYPE: Clinical, EEG

COMPOUND: 8 quinolinol,5-Chloro-7-iodo-
000130267

REFERENCE: Jones, E.L., Searle, C.E. and Smith, W.T.
Acta Neuropath. 24:256-262, 1973.

OBSERVED NEUROTOXIC EFFECTS: Unsteady gait to hindlimb paralysis early as 114 wk In paralyzed rats sciatic nerves more damaged than brachial. Loss of myelinated fibers, Wallerian degeneration; patchy vacuolization throughout cord white-matte. (authors say possibly artifact), and degeneration in gracile fasciculi of posterior columns that looked like ascending demyelination. In 1 rat brain necrosis in thalamus and central white-matter. Mild peripheral lesions. Some lesions in controls. Optic nerves all intact.

ANIMALS: Rats, Wistar, 12 M and 8 F, age 7 wk.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1% in diet of maize, intake approx. 50 mg/kg.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 6M, 6F maize diet only.

DURATION OF EXPERIMENT: Serial sacr to 132 wk.

EXAM. TYPE: Behavior, histology

COMPOUND: 8-Quinolinol, 5-chloro-7-iodo-

000130267

REFERENCE: Tateishi, J., Ikeda, H., Saito, A., Kuroda, S. and Otsuki, S. Neurology 22:702-709, 1972.

OBSERVED NEUROTOXIC EFFECTS: Acute: death with convulsions. Chronic: ataxia, hindlimb motor paralysis after 20-28 d, symmetrical degeneration of long tracts of cord and spinal rrot ganglia.

ANIMALS: 11 Dogs: 8 treated (2 grps), 3 controls

PREPARATION AND DOSE
or HISTORY OF PATIENT: 72-125 mg/kg/d for 1.5-62 d; 56-128 mg/kg/d with constipating drugs for 2-64 d.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 2 dogs untreated, 1 given constipating drugs only

DURATION OF EXPERIMENT: About 2 mo.

EXAM. TYPE: Behavior, histology

533^

COMPOUND: 8 quinolinol,5-Chloro-7-iodo-

000130267

REFERENCE: Tateishi, J., Kuroda, S., Saito, A. and Otsuki, S. Acta Neuropath. 24:304-320, 1973.

OBSERVED NEUROTOXIC EFFECTS: Some died with acute convulsions, others developed muscle weakness judged by gait, 3 dogs showed no signs. Distal degeneration in posterior cord and optic tract; axons, then demyelination, then spinal root ganglia, and peripheral nerves. Both strain and specific differences reported.

ANIMALS: Dogs: 20 mongrels, 8 purebred F beagles aged 14 mo, 27 cats, 1 monkey.

PREPARATION AND DOSE
or HISTORY OF PATIENT:
(1) 20 Mongrels: Japanese-made clioquinol suspened in milk, 2 x d.
(2) 4 Beagles: Japanese-made, twice daily.
(3) 4 Bealges: Swiss-made compound, twice daily.
(4) 22 Cats: Compound in food.
(5) Monkey: Water suspension Japanese-made compound once daily.

ROUTE AND SITE: Oral or nasal tube (monkey)

CONTROL INFORMATION: 4 mongrels, 4 beagles, 5 cats, 1 monkey.

DURATION OF EXPERIMENT: 1-383 d

EXAM. TYPE: Behavior, histology

534

COMPOUND: 8-Quinolinol, 5-chloro-7-iodo-

000130267

REFERENCE: Tsubaki, T., Honma, Y. and Hoshi, M.
Lancet i:696-697, 1971.

OBSERVED NEUROTOXIC EFFECTS: Of 110 given compound for >14 d 35.4% had neuropathy; of 153 given it for <13 d, 2.6% had neuropathy; controls 0%. Symptoms: leg paresthesia, gait, and signs identical with subacute myelo-optico-neuropathy (includes axonal damage and demyelination of optic nerve).

ANIMALS: 263 Humans

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.6-1.6 g/d as treatment to patients with digestive disorders.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 706 disorder-matched patients not given the compound.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Clinical

COMPOUND: 8-Quinolinol, copper(II)chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 67 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinol, 4,5'-dichloro-3'-hydroxy-2'-napthoate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 350 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

535

COMPOUND: 8-Quinolinol, 5-iodo-4'-chloro-3'-hydroxy-2'-napthoate, copper(II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 110 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

536

COMPOUND: 8-Quinolinolium 7'-bromo-3'-hydroxy-2'naphthoate, copper (II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 26 mg/kg in 0.5% methylcellulose

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinolium 4',7'-dibromo-3'-hydroxy-2'-naphthoate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 85 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinolium 4', 7'-dibromo-3'-hydroxy-2'-naphthoate, copper(II)chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 39 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

5337

COMPOUND: 8-Quinolinolium 1'-hydroxy-2'-naphthoate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 72 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

5380

COMPOUND: 8-Quinolinolium 3'-hydroxy-2'-naphthoate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}:61 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinolium 1'-hydroxy-2'-naphthoate, copper (II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 27 mg/kg in 0.5% methylcellulose

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: 8-Quinolinolium 3'-hydroxy-2'-naphthoate, copper (II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 23 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

539

COMPOUND: 8-Quinolinolium salicylate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE or HISTORY OF PATIENT: LD_{50}: 58 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk

EXAM. TYPE: Clinical.

540

COMPOUND: 8-Quinolinolium salicylate, copper (II) chelate

REFERENCE: Bernstein, E.H., Pienta, P.W. and Gershon, H.
Tox. Appl. Pharm. 5:599-604, 1963.

OBSERVED NEUROTOXIC EFFECTS: This study included 8-quinolinol, selected salts and copper chelates. 8-quinolinol was shown to be more toxic than its salts. The introduction of the copper chelate decreased the toxicity of 8-quinolinol, but increased the toxicity of the derivatives. The salts, generally, manifested their toxicities within 72 hours. The toxic reactions to the chelates were, generally, more delayed. Some of these compounds appear to show sex specificity in their toxic manifestations. Symptoms included: confusion, respiratory difficulty, convulsions and some paralysis.

ANIMALS: Mice, Swiss, random-bred albino, 18-22 g
10 animals per dose level, 5 M and 5 F.

PREPARATION AND DOSE
or HISTORY OF PATIENT: LD_{50}: 13.1 mg/kg in 0.5% methylcellulose.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 10 controls treated with methyl cellulose.

DURATION OF EXPERIMENT: At least 3 wk.

EXAM. TYPE: Clinical.

COMPOUND: Reserpine phosphate

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced depression and associated slow-wave EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1-5 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Resorcinol, 2-p-mentha-1,8-dien-3-yl-5-pentyl-

REFERENCE: Christensen, H.D., Freudenthal, R.I., Gidley, J.T., Rosenfeld, R., Boegli, G., Testino, L., Brine, D.R., Pitt, C.G. and Wall, M.E. Science 172: 165-167, 1971.

OBSERVED NEUROTOXIC EFFECTS: The biological activity of the above compound, and other cannabinoids was compared to that of Δ^9-Tetrahydrocannabinol. Similar neurological and behavioral responses were found for all, provided that high concentrations were given. The potency of the compounds varied depending on structure and route of administration. Behavioral pattern was characterized by irritability, decrease in activity, reduced sensorimotor responses. Intracerebral admin. increased potency.

ANIMALS: Mice

PREPARATION AND DOSE or HISTORY OF PATIENT: Amount ns., table included comparing relative potency of Δ^9THC to compound tested.

ROUTE AND SITE: I.V. or Intracerebral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

541<

COMPOUND: Resorcinol, 2-p-mentha-1,8-dien-3-yl-5-pentyl-

REFERENCE: Karler, R., Cely, W. and Turkanis, S.A. Res. Comm. Chem. Path. Pharm. 7(2):353-358, 1974.

OBSERVED NEUROTOXIC EFFECTS: Bar-walk test gave decreasing order of toxicity as dimethylheptylpyran, Δ^9-tetrahydrocannabinol, cannabidiol; anticonvulsant and "toxic" actions concluded to be separable.

ANIMALS: Mice, ICR, 4-5 wk old

PREPARATION AND DOSE or HISTORY OF PATIENT: 100-200 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Own controls

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior

542

COMPOUND: Retinol, all trans-
000068268

REFERENCE: Langman, J. and Welch, G.W.
J. Comp. Neurol. 128: 1-16, 1966.

OBSERVED NEUROTOXIC EFFECTS: Anencephaly and/or myeloschisis was observed in 26% of the implanted rat embryos after 3 x 10^4 USP units (most effective dose); mouse results were inconsistent. The internal limiting membrane for diencephalon and mesencephalon was disrupted at day 12, with displacement of tissue and then degeneration. The neural groove was prevented from closing.

ANIMALS: (1) Rats, Wistar, F, 200-250 g, bred
(2) Mice, Swiss Webster, F, bred

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Rats: 3-6 x 10^4 USP units on d 8,9,10 of gestation
(2) Mice: 3-7.5 x 10^3 USP units/d, 1-3 doses, d 7-9 of gestation.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: (1) Rats: vehicle or saline.
(2) Mice: none.

DURATION OF EXPERIMENT: Serial, to term.

EXAM. TYPE: Teratology

COMPOUND: Retinol, all trans-
000068268

REFERENCE: Langman, J. and Welch, G.W.
J. Comp. Neurol. 131: 15-26, 1967.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused interference with the mitosis of neuroepithelial cells bordering the neural groove in embryos, resulting in exencephaly and anencephaly at birth. Upon treatment, fewer cells were formed and existing cells degenerated; differentiation of developing cells was affected; abnormal behavior was also observed.

ANIMALS: Mice, Swiss-Webster, 23-28 g, F.

PREPARATION AND DOSE or HISTORY OF PATIENT: 10,000 USP units/d on d 14 and 15 of gestation or for 2-3 d starting d 11

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated with compound

DURATION OF EXPERIMENT: 1 hr to full-term

EXAM. TYPE: Histology, behavior

COMPOUND: Salicylic acid, monosodium salt

000054217

REFERENCE: Ryder, H.W., Shaver, M. and Ferris, E.B.
New Eng. J. Med. 232:617-621, 1945.

OBSERVED NEUROTOXIC EFFECTS: Toxic encephalopathy (6 hr postmortem), cortical edema, pyramidal degeneration extending to basal ganglia, substantia nigra and brainstem. Excesses of microglia, swollen oligodendroglia in white-matter. Other damage secondary to hemorrhages. Clinical evidence of salicylate toxicity included hyperpnea and respiratory alkalosis.

ANIMALS: Human: 1 case, F, 16 yr

PREPARATION AND DOSE or HISTORY OF PATIENT: 26 g given over 6 d in hospital (0.7 g/kg) and death occured on d 8. Autopsy disclosed active rheumatic heart disease.

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 8 d

EXAM. TYPE: Clinical, autopsy

543

COMPOUND: Saxitoxin

REFERENCE: Bull, R.J. and Trevor, A.J.
J. Neurochem. 19:999-1009, 1972.

OBSERVED NEUROTOXIC EFFECTS: Inhibited increase of lactate and redistribution of sodium and potassium from electrical stimulation in vitro.

ANIMALS: Rats, S-D, M, 200-250 g, brain cortex slices in vitro.

PREPARATION AND DOSE or HISTORY OF PATIENT: 10^{-7} - 10^{-8} M in incubation medium.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Biochemistry

5547

COMPOUND: Saxitoxin

REFERENCE: Narahashi, T., Haas, H.G. and Therrien, E.F.
Science 157: 1441-1442, 1967.

OBSERVED NEUROTOXIC EFFECTS: Saxitoxin blocks conduction with no change in resting potential. The mechanism of the blockage is similar to that caused by tetrodotoxin, but recovery of washed axons is faster.

ANIMALS: Lobster (Homarus americanus)

PREPARATION AND DOSE
or HISTORY OF PATIENT: Partly isolated giant axons treated with saxitoxin at 3×10^{-8} to 3×10^{-7} moles/liter of medium.

ROUTE AND SITE: Semi-in vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Up to 100 min

EXAM. TYPE: Electrophysiology

COMPOUND: Scopolamine

000051343

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.G., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Scopolamine bromide

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: Compound produced locomotor ataxia and arousal EEGs.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 2-4 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

545>

COMPOUND: Semicarbazide
000057567

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.6 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

5496

COMPOUND: Semicarbazide, 4,4-diethyl-, hydrochloride

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.66 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Semicarbazide, thio-
000079196

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122:110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1) 0.15 mM/kgm
2) 0.14 mM/kgm

ROUTE AND SITE: (1) I.P.; (2) I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

COMPOUND: Semicarbazide, thio-
000079196

REFERENCE: Knyihar, E., Kiss, J. and Csillik, B.
Res. Comm. Chem. Path. Pharm. 2: 392-405, 1971.

OBSERVED NEUROTOXIC EFFECTS: This semicarbazide produced typical convulsions after 30-45 min at which time the label was concentrated in the hippocampus glial cells. The authors inferred that thiosemicarbazide-sensitive enzymes for GABA metabolism are located at glio-neuronal interfaces.

ANIMALS: 8 Rats, R-Amsterdam, 150 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 20 mg/kg, labeled

ROUTE AND SITE: I.P.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 55 min

EXAM. TYPE: Behavior, autoradiography (histological)

547<

COMPOUND: Semioxamazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1.8 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

548

COMPOUND: Senna

REFERENCE: Steer, H.W. and Colin-Jones, D.G.
J. Path. 115:199-205, 1975

OBSERVED NEUROTOXIC EFFECTS: More lysosomal activity and lysosomes in Schwann cells and neurons of submucosal plexus of colonic mucosa.

ANIMALS: Human: 7 aged 24-80 with melanosis coli who took purgatives; 1 who had taken purgatives for only 1 m.

PREPARATION AND DOSE or HISTORY OF PATIENT: Rectal biopsy before and 3-7 m after stopping medication

ROUTE AND SITE: Oral

CONTROL INFORMATION: 7 aged 27-70 with other gut disorders who had taken no purgatives for 3 m.

DURATION OF EXPERIMENT: About 7 m.

EXAM. TYPE: Histology, histochemistry

COMPOUND: Serine, dihydrogen phosphate (ester), L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Shigella Shigae toxin

REFERENCE: Masek, K., Smetana, R. and Raskova, H.
Int. J. Neuropharmacol. 1: 71-77, 1962.

OBSERVED NEUROTOXIC EFFECTS: The mice exhibited a dose-related depression of brain norepinephrine after a 48-hr lag period. Brain serotonin was also depressed.

ANIMALS: Mice, Konarovice, M and F, 16-18 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.2×10^{-6} to 0.4×10^{-4} ml/mouse

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Yes, but not described.

DURATION OF EXPERIMENT: Serial 6-48 hr

EXAM. TYPE: Biochemistry

549

COMPOUND: Sodium azide
026628228

REFERENCE: Mettler, F.A. and Sax, D.S.
Brain 95:505-516, 1972.

OBSERVED NEUROTOXIC EFFECTS: Acute syndrome giving ataxia due to cerebellar cortical destruction (authors state that subacute effects are well known and chronic effects less well known), claimed first description.

ANIMALS: 11 Rhesus monkeys

PREPARATION AND DOSE or HISTORY OF PATIENT: 8-16 mg/kg one dose; followed by other trtmts; pretrtmt with thiamytal or succinylcholine chloride before NaN_3, or oil of wormwood instead of NaN_3.

ROUTE AND SITE: I.V., saphenous vein at ankle

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Approx 1 hr/experiment

EXAM. TYPE: Behavior, histology

550

COMPOUND: Sodium azide
026628228

REFERENCE: Miyoshi, K.
Acta Neuropathol. 9:199-216, 1967.

OBSERVED NEUROTOXIC EFFECTS: Selective vulnerability of basal ganglia to striatal necrosis. Necrosis in corpus striatum (35 rats), pallidum (13 rats), cortex (5); demyelination of optic tract (7). Diffuse and complete loss of oxidative enzyme activities, in necrotic tissues.

ANIMALS: Rats, albino, 110-130 g, 64 used.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.1% dilutions, 3 mg/kg, 4/d at 30 min intervals, in 50 rats for 4 d.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: na.

DURATION OF EXPERIMENT: Serial sacr: 14 rats within 24 hr, 50 rats 3-50 d after last dose.
EXAM. TYPE: Histology, histochemistry

COMPOUND: Stannane, acetoxytriphenyl-
000900958

REFERENCE: Verschuuren, H.G., Kroes, R., Vink, H.H., and Van Esch, G.J.
Food Cosmet. Toxicol. 4: 35-45, 1966.

OBSERVED NEUROTOXIC EFFECTS: Doubtful edema in spinal cord in 3 rats on 10 ppm, 2 on 25 ppm and 1 on 50 ppm accompanying increase in water content of the brain and spinal cord. Doubtful edema in brain of 1 guinea-pig on 5 ppm and 1 on 50 ppm. Brain weights increased in guinea-pigs with 20 ppm.

ANIMALS: For each experiment, 4-6 groups of 20 or more animals, 1/2 F, 1/2 M:
Rats, Wistar, 4 wk old, 40-60 g.
Guinea-pigs, albino, 3 wk old, 130-200 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0,5,10,25 and 50 ppm in rats.
0,5,10,20 and 50 ppm in guinea-pigs.

ROUTE AND SITE: Oral

CONTROL INFORMATION: na

DURATION OF EXPERIMENT: 6-90 day studies for 1 1/2 yr

EXAM. TYPE: Behavior, pathology, histology

COMPOUND: Stannane, chlorotriethyl-

REFERENCE: Robinson, I.M.
Fd. Cosmet. Toxicol. 7: 45-52, 1969

OBSERVED NEUROTOXIC EFFECTS: Treatment caused hindlimb paralysis, depression, death; lowered brain epinephrine, norepinephrine and serotonin for 48 hours.

ANIMALS: Rats, Osborne-Mendel, F, 190-220 g, 18/group

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg in corn oil

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Equivalent corn oil

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Behavior, biochemistry

5514

COMPOUND: Stannane, dibutyloxo-

000818086

REFERENCE: Robinson, I.M.
Fd. Cosmet. Toxicol. 7: 45-52, 1969

OBSERVED NEUROTOXIC EFFECTS: Treatment lowered brain epinephrine, norepinephrine and serotonin for 48 hours.

ANIMALS: Rats, Osborne-Mendel, F, 190-220 g, 18/group

PREPARATION AND DOSE
or HISTORY OF PATIENT: 80 mg/kg in corn oil

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Equivalent corn oil

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Behavior, biochemistry

552

COMPOUND: Stannane, hydroxytriethyl-

REFERENCE: Vershuuren, H.G., Kroes, R., Vink, H.H. and Van Esch, G.J. Food Cosmet. Toxicol. 4: 35-45, 1966

OBSERVED NEUROTOXIC EFFECTS: Paralysis and protonation of hindlegs observed in 3-8 wk old rats at 10, 20 ppm and 1-3 wk old guinea-pigs. Alopecia in 2 rats given 10 ppm. Induced interstitial edema in brain and spinal cord of rats.

ANIMALS: For each experiment, 4-6 groups of 20 or more animals, 1/2 F, 1/2 M.
Rats, Wistar, 4 wk old, 40-60 g.
Guinea-pigs, Albino, 3 wk old, 130-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0,5,10,20 ppm in rats
0,5,10,20 ppm in guinea-pigs

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 6-90 d studies for 1 1/2 yr.

EXAM. TYPE: Behavior, pathology, histology

COMPOUND: Stannane, hydroxytriphenyl-
000076879

REFERENCE: Verschuuren, H.G., Kroes, R., Vink, H.H., and Van esch, G.J Food Cosmet. Toxicol. 4: 35-45, 1966

OBSERVED NEUROTOXIC EFFECTS: Paralysis and protonation of hindlimb. Doubtful edema in spinal cord of 3 rats on 10 ppm, 2 on 25 ppm and 1 on 50 ppm accompanying increase in water content of brain and spinal cord. Doubtful edema in brain of 4 guinea-pigs on 20 ppm and 2 on 50 ppm.

ANIMALS: For each experiment, 4-6 groups of 20 or more animals, 1/2 F, 1/2 M.
Rats, Wistar, 4 wk old, 40-60 g.
Guinea-pigs, Albino, 3 wk old, 130-200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0,5,10,25 and 50 ppm in rats.
0,2.5,5,10,20 and 50 ppm in guinea-pigs.

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 6-90 d studies for 1 1/2 yr

EXAM. TYPE: Behavior, pathology, histology

COMPOUND: Stannane, triethyl-

REFERENCE: Hirano, A., Dembitzer, H.M., Becker, N.H. and Zimmerman, H.M. J. Neuropath. Exp. Neurol. 28(3):507-511, 1969.

OBSERVED NEUROTOXIC EFFECTS: Splitting of myelin sheath in the central nervous system.

ANIMALS: Rats, Albino; 200-300 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg/kg x 1.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Sacr at 24 hr.

EXAM. TYPE: Histology, Histochemistry, Ultrastructural

553

COMPOUND: Stannane, triethyl-

REFERENCE: Levy, W.A., Taylor, J.M., Herzog, I. and Scheinberg, L.C. Arch. Neurol. 13:58-64, 1965.

OBSERVED NEUROTOXIC EFFECTS: Diffuse edema of cerebral white matter with diffuse splitting and distension of the myelin sheaths. Urea diminished intensity of tin effects.

ANIMALS: Rabbits, NZ White, 2.5-3.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5% in a dose of 1 mg/kg, 1/d for 6 d, followed on d 6 by urea, 30% soln i.v., 4 gm/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Controls treated with urea only.

DURATION OF EXPERIMENT: Serial sacr to 6 hr.

EXAM. TYPE: Histology, biochemistry

554

COMPOUND: Stannane, triethyl-

REFERENCE: Magee, P.N., Stoner, H.B. and Barnes, J.M.
J. Path. Bact. 73:107-124, 1957.

OBSERVED NEUROTOXIC EFFECTS: Reversible interstital edema of brain and cord white-matter without gross neuronal damage.

ANIMALS: Rats, Porton, age 30-70 d.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Acute: triethyltin sulfate 10 mg/kg, dichloride 20 mg/kg.
Chronic: 20 ppm in diet 14 d, then 10 ppm.

ROUTE AND SITE: Acute: I.P. Chronic: Oral

CONTROL INFORMATION: Pair fed groups.

DURATION OF EXPERIMENT: Up to 5 mo.

EXAM. TYPE: Biochemistry, histology

COMPOUND: Stannane, triethyl-

REFERENCE: Smith, M.E.
J. Neurochemistry 21:357-372, 1973.

OBSERVED NEUROTOXIC EFFECTS: Brain and spinal cord edema, paralysis and death. Spinal cord more edematous than brain. Severe myelin loss. Swelling of astrocytes, axons and cleft development in myelin. Brain myelin loss 16% in M, 25% in F.

ANIMALS: Rats, Wistar, M and F, 2 mo. age.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/l/d in drinking water.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Matched control water ttd.

DURATION OF EXPERIMENT: Serial sacr 7-11 wk.

EXAM. TYPE: Histology, Histochemistry, Ultrastructural

COMPOUND: Stannane, triethyl-

REFERENCE: Torack, R., Gordon, J. and Prokop, J.
Int. Rev. Neurobiol. 12:45-86, 1970.

OBSERVED NEUROTOXIC EFFECTS: Weakness, stupor in all except the 4 mg/kg group, 9 mg/kg was fatal. Cerebral edema, especially of corpus callosum; swollen astrocytes, focal dilatation of axons, oligodendrites not affected. Reduced ATPase activity. Fluid accumulation. Splitting of myelin sheaths.

ANIMALS: (1) Rats, albino, M, 300-350 g.
(2) Rats, S-D, 375-425 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 4-9 mg/kg, single dose.
(2) 7 mg/kg, single dose, with labeled substrates; 1 mg/kg/d for 7-10 d (1 grp).

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Normal rats

DURATION OF EXPERIMENT: Serial sacr (1) 6-24 hr (2) 4-22 hr or 7-10 d

EXAM. TYPE: Biochemistry, histology

555

COMPOUND: Strychnine
000057249

REFERENCE: Johnston, G.A.R. and Mitchell, J.F.
J. Neurochem. 18:2441-2446, 1971.

OBSERVED NEUROTOXIC EFFECTS: All four compounds influenced the release of GABA, but not its uptake. Biculline, at 10^{-5} M (not more or less) potentiated evoked release of GABA but not the resting release. Metrazol inhibited the electrically resting release but not the electrically evoked release. Strychnine and picrotoxin inhibited the electrically evoked release of GABA.

ANIMALS: In vitro slices of rat cerebral cortex

PREPARATION AND DOSE or HISTORY OF PATIENT: Preincubated with compounds for 15 min, then with labeled GABA for 10 min.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: 25 min

EXAM. TYPE: Biochemistry

556

COMPOUND: Strychnine
000057249

REFERENCE: Yagi, K. and Sawaki, Y.
Brain Res. 84:155-159, 1975.

OBSERVED NEUROTOXIC EFFECTS: Rat hypothalamus tuber-infundibular neurons (controlling adenohypophysis functions) were recurrently facilitated in presence/absence of compound. No effects, suggesting that this neural circuit is resistant to compound.

ANIMALS: Rats, Wistar, F cyclic, 191-340 g, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.2 mg/kg and up to 0.5 mg/kg.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Control 0.4 ml of gallamine triethiodide soln (2% w/v) or Locke's soln, repeatedly inj.

DURATION OF EXPERIMENT: Various short-term intervals.

EXAM. TYPE: Electrophysiological

COMPOUND: Strychnine, sulfate (2:1)
000060413

REFERENCE: Luse, S.A., Goldring, S. and O'Leary, J.
Arch. Neurol. 11:296-302, 1964.

OBSERVED NEUROTOXIC EFFECTS: 82% of 50 cortical neurons had marked dilation of ergastoplasmic sacs of perikaryon and dendrites; controls showed only occasional edema.

ANIMALS: 6 Rabbits, 1.5-2 kg, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.5-3.5 mg/rabbit.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Same animals, biopsy and recordings before compound; also doses of 4 other convulsive compound.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, electrophysiology, histology

COMPOUND: Strychnine, sulfate (2:1)
000060413

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: This compound produced convulsions and a desynchronized EEG.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.25-1 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

557

COMPOUND: Succinamic acid, alpha-amino-, L-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glucamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

558A

COMPOUND: Succinamic acid, alpha-amino-, L-

REFERENCE: Olney, J.W., Ho, O.L. and Rhee, V.
Exp. Brain Res. 14:61-76, 1971.

OBSERVED NEUROTOXIC EFFECTS: No cytotoxicity was observed.

ANIMALS: Mice, Swiss-webster age 10 d, total 250

PREPARATION AND DOSE
or HISTORY OF PATIENT: Initially 12 mmoles/kg, then range established for each compound.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Compounds compared with monosodium L-glutamate (MSG) potency for selectively necrosing neurons in retina and brain (hypothalamus)

DURATION OF EXPERIMENT: 5 hr or serial intervals including 5 hr.

EXAM. TYPE: Histology

COMPOUND: Succinic acid
000110156

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

COMPOUND: Succinic acid, 2-aminomethyl-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to expose motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

559

COMPOUND: Succinic acid, 2,3-diamino-, meso-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE
or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, ionophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

560

COMPOUND: Succinic acid, mercapto-,diethyl ester, S-ester with 0,0-dimethyl phosphorodithioate
(Malathion)
000121755

REFERENCE: Casida, J.E., Baron, R.L., Eto, M. and Engel, J.L.
Biochem. Pharm. 12: 73-83, 1963.

OBSERVED NEUROTOXIC EFFECTS: Malathion was potentiated by: triphenyl phosphates and phosphonates with o- and p-, methyl and ethyl substituents; some diphenylphosphonates and N-methyl phosphoramidates; S,S,S,-trialkyl phosphorotrithioites and phosphorotrithioates; saligenic cyclic P esters. The last two groups produced ataxia readily in hens.

ANIMALS: Mice, Rolfsmeyer, F, 25 g
Hens, White Leghorn, 6-18 mo, 1.4-2.2 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: Tests to determine effect of various compounds in malathion toxicity and antiesterase activity.
Hens: Acute lethal and minimal ataxia dosages studied.

ROUTE AND SITE: I.P. (mice); I.P. or oral (hens).

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Mortality, clinical, in vitro biochemical

COMPOUND: Succinic acid, mercapto-, diethyl ester, S-ester with 0,0-dimethyl phosphorodithioate
000121755

REFERENCE: Gaines, T.B.
Tox. Appl. Pharm. 14: 515-534, 1969.

OBSERVED NEUROTOXIC EFFECTS: 1000 mg/kg produced leg weakness

ANIMALS: Chickens, White Leghorn, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 15 mg/kg atropine sulfate orally 15 min prior to compound; graded doses compound in peanut oil

ROUTE AND SITE: S.C., under right wing

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 1 yr

EXAM. TYPE: Clinical

COMPOUND: Succinic acid, mercapto-, diethyl ester, S-ester with O,O-dimethyl phosphorodithioate

000121755

REFERENCE: Murphy, S.D., Lauwerys, R.R. and Cheever, K.L.
Tox. Appl. Pharm. 12: 22-35, 1968.

OBSERVED NEUROTOXIC EFFECTS: Poor inhibitor of brain cholinesterase. Metabolized to malaoxon which is an inhibitor.

ANIMALS: Mice, Swiss-Webster, M, 25-30g
Chickens, White Rock X N.H. Red, M, 500-700g
Sunfish, M and F, 40-80g
Bullfish, M and F, 40-80g

In vitro brains of rats, guinea pigs, sparrows, smallmouth bass, flounder, sculpin and monkey.

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.1-1500 mg/kg, various schedules (I.P.) in mice, chickens, sunfish and bullheads; 0.1-200 mg/kg (orally) in sunfish; 0.001-4 picomoles of malaoxon in vitro.

ROUTE AND SITE: See above

CONTROL INFORMATION: Brain cholinesterase determined in controls

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Biochemistry

5613

COMPOUND: Succinic acid, mercapto-, diethyl ester, S-ester with O,O-dimethyl phosphorodithioate

000121755

REFERENCE: Rayner, M.D., Popper, H.S., Carvalho, E.W. and Hurov, R.
Res. Comm. Chem. Path. Pharm. 4: 595-606, 1972.

OBSERVED NEUROTOXIC EFFECTS: The force generated by the achilles tendon reflex was subnormal in exposed subjects. The authors suggest that this hyporeflexia may be a sensitive indicator of chronic exposure to organophosphates.

ANIMALS: Humans, Japanese ancestry, M, ages 22-59 (orchid farmers)

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure of more than 4 hr/d, 2 d/wk, 52 wk/yr for 5 yr except one case (2 yr). Other types of pesticide also used, but authors judged organophosphates exposures to be primary.

ROUTE AND SITE. Skin contact, inhalation

CONTROL INFORMATION: Matched non-exposed subjects, so far as could be ascertained

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Physiological

562

COMPOUND: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-

REFERENCE: DeRobertis, E., Sellinger, O.Z., Arnais, G.R. deL., Alberici, M. and Zieher, L.M.
J. Neurochem. 14:81-89, 1967.

OBSERVED NEUROTOXIC EFFECTS: Mode-of-action study. Most bound drug was in the mitochondrial fraction. Some increase of activity of catechol-O-methyltransferase; strong inhibition of alanine aminotransferase and glutamine synthetase (especially in synaptic membranes). Ultrastructure changes included swollen nerve-endings and loss of synaptic vesicles. Authors conclude an action on glutamate-glutamine-GABA metabolism in nerve-endings.

ANIMALS: Rats, white, adult, 150 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.15 ml of solution containing 8.7 mg/mg (labeled), to produce convulsions.

ROUTE AND SITE: Intrathecal

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 1-1.5 hr

EXAM. TYPE: Brain cortex fractions studied in vitro.

COMPOUND: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl

REFERENCE: Harris, B.
Arch. Neurol. 11:388-407, 1964.

OBSERVED NEUROTOXIC EFFECTS: Cortex but not white-matter was vacuolated after 1-4 hr of seizures; vacuoles contained osmiophilic granules, which was also found in distended cytoplasm between inner myelin lamellae and axons.

ANIMALS: Rabbits and dogs, adults, surgically prepared

PREPARATION AND DOSE or HISTORY OF PATIENT: Rabbits: 1 g, dogs: 5 g (per animal).

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Rabbits, normals, and treated in various ways.

DURATION OF EXPERIMENT: About 30 min per experiment.

EXAM. TYPE: Behavior, electrophysiology, histology

COMPOUND: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-

REFERENCE: Lamar, C., Jr. and Sellinger, O.Z.
Biochem. Pharm. 14:489-506, 1965.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced inhibition of cerebral cortex glutamine synthetase and glutamine transferase within 30 minutes. The degree of inhibition was progressive with time. Rats not sacrificed in 4 hours experienced convulsions.

ANIMALS: Rats, Holtzman, M, 150-200 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 400 mg/kg followed by serial sacrifice up to 4 hr.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 4 hr

EXAM. TYPE: Biochemistry

593

COMPOUND: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-

REFERENCE: Rizzuto, N. and Gonatus, N.K.
J. Neuropath. Exp. Neurol. 33(2):237-250, 1974

OBSERVED NEUROTOXIC EFFECTS: Ataxia, weakness, seizures. After severe and prolonged seizures there was clearing and swelling of 10% presynaptic endings and glial edema. Alteration of presynaptic terminals suggested as metabolic effect of seizures rather than direct drug-effect. Administration to developing rats did not result in seizures or morphological changes in presynaptic terminals, some glial swelling.

ANIMALS: Rats, Osborne-Mendel, M and F (1) 8 adults, (2) 2 adults, (3) 2 ten-d old, (4) 3 developing rats.

PREPARATION AND DOSE or HISTORY OF PATIENT:
(1) 400-600 mg/kg, single convulsant dose.
(2) 100 mg/kg, two subconvulsant doses at 24 hr intervals.
(3) Single adult convulsant dose
(4) 100 mg/kg, daily from birth to 24th d.

ROUTE AND SITE: (1-3) I.P. (4) S.C.

CONTROL INFORMATION: (1) 3 controls, (2) 2 controls, (3) 1 control, (4) 2 control rats.

DURATION OF EXPERIMENT: Serial sacr various time intervals.

EXAM. TYPE: Behavior, ultrastructural, histopathological

5947

COMPOUND: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-

REFERENCE: Sinden, S.L., Durbin, R.D., and Uchytil, T.F.
Toxic. Appl. Pharmac. 14: 82-88, 1969.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions with minimal dose of 0.25 mmoles/kg I.P. and became uncoordinated and then spastic.
(2) Convulsions with minimal dose of .00038 mmoles/kg.

ANIMALS: (1) Mice, weanling Swiss Webster, 10g
(2) Rats, Holtzman, 135g

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) 0.25-4.0 mmoles/kg I.P.
(2) .0015-.006 mmoles/kg intracisternally.

ROUTE AND SITE: I.P. and intracisternally.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 2-10 hrs. I.P.; 60-75 mins. intracisternally.

EXAM. TYPE: Behavior

COMPOUND: Tellurium

REFERENCE: Duckett, S.
Exp. Neurol. 31:1-16, 1971.

OBSERVED NEUROTOXIC EFFECTS: 24 of 30 produced litters, 20 litters all hydrocephalic, 6 litters all normal. Pathology mainly in ependyma and subependyma, later the white-matter of survivors is edematous, cortex gradually destroyed, and connective tissue present.

ANIMALS: 30 Rats, Wistar, F, mated

PREPARATION AND DOSE or HISTORY OF PATIENT: 3000 ppm in diet fed through gestation.

ROUTE AND SITE: Oral

CONTROL INFORMATION: 20 similar controls.

DURATION OF EXPERIMENT: Pregnancy

EXAM. TYPE: Teratology

COMPOUND: Tellurium

REFERENCE: Lampert, P., Garro, F. and Pentschev, A.
Acta Neuropath. 15:308-317, 1970.

OBSERVED NEUROTOXIC EFFECTS: Segmental demyelination of sciatic nerves and spinal roots resulting in hindlimb paralysis. Edema of nerves and vacuolar degeneration of Schwann cells, followed by disintegration and removal of myelin segments. Recovery from paralysis and remyelination occurred despite continued treatment. Group treated at 20 d age showed less hind leg weakness, than those treated at 17 d age.

ANIMALS: Rats, Long-Evans, 21 from different litters, weanlings.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 1% in diet

ROUTE AND SITE: Oral

CONTROL INFORMATION: 4 rats

DURATION OF EXPERIMENT: 25 d

EXAM. TYPE: Behavior, histology

565

COMPOUND: Tellurium tetrachloride

REFERENCE: Carlton, W.W. and Kelly, W.A.
Tox. Appl. Pharm. 11:203-214, 1967.

OBSERVED NEUROTOXIC EFFECTS: Necrosis in cerebral cortex, brain lesions. Focal neuronal rarefaction and extensive thinning of cortical tissue.

ANIMALS: Drakes, Pekin, 1 d old

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50-1000 ppm in diet.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Weight and species matched, untreated.

DURATION OF EXPERIMENT: Up to 4 wks.

EXAM. TYPE: Necropsy, histology

566

COMPOUND: Tetanus toxin

REFERENCE: Fedinec, A.A. and Shank, R.P.
J. Neurochem. 18:2229-2234, 1971.

OBSERVED NEUROTOXIC EFFECTS: Local and generalized tetany ran its course. No changes in levels of glycine, GABA, glutamate, aspartate, or other amino acids in cord or either half of it, so that the amino acid pool was stable throughout. Authors conclude that if glycine is a spinal inhibitory neurotransmitter released by tetanized interneurons, then the toxin should interfere with its release rather than deplete the pool.

ANIMALS: Rats, Wistar, M, 250-350 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 10^{-4} mouse MLD/kg in 5 mcl 0.15 M-NaCl/dose, one dose.

ROUTE AND SITE: I.M., left gastrocnemius

CONTROL INFORMATION: 3 non-injected rats

DURATION OF EXPERIMENT: Serial to 45 hr.

EXAM. TYPE: Biochemistry, behavior

COMPOUND: Tetanus toxin

REFERENCE: Webster, R.A.
Int. J. Neuropharmacol. 6: 207-215, 1967.

OBSERVED NEUROTOXIC EFFECTS: The toxin exaggerated polysynaptic but not monosynaptic reflexes. In ventral root and motor nerve filaments, alpha but not gamma motorneurones became more excitable. No increase of afferent input from muscle spindles was observed. The author concluded that the toxin acted by abolishing inhibitions of alpha motorneurones.

ANIMALS: Rabbits, no details, surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1250 mouse m.l.d.

ROUTE AND SITE: I.M., left gastrocnemius

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Electromyography

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro- (Metrazol)

000054955

REFERENCE: Johnston, G.A.R. and Mitchell, J.F.
J. Neurochem. 18:2441-2446, 1971.

OBSERVED NEUROTOXIC EFFECTS: All four compounds influenced the release of GABA, but not its uptake. Biculline, at 10^{-5} M (not more or less) potentiated evoked release of GABA but not the resting release. Metrazol inhibited the electrically resting release but not the electrically evoked release. Strychnine and picrotoxin inhibited the electrically evoked release of GABA.

ANIMALS: In vitro slices of rat cerebral cortex

PREPARATION AND DOSE or HISTORY OF PATIENT: Preincubated with compounds for 15 min, then with labeled GABA for 10 min.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Lab

DURATION OF EXPERIMENT: 25 min

EXAM. TYPE: Biochemistry

56?<

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro

000054955

REFERENCE: Nahorski, S.R., Roberts, D.J. and Stewart, G.G.
J. Neurochem. 17: 621-631, 1970.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused irregular clonus of the forehead and limbs 75-90 sec after treatment, progressing to the rest of body and to tonic flexion; about 100 sec after treatment, a full tonic extensor seizure lasted 10 sec; then sedation with death or recovery in 20 min. Levels of 25 brain metabolites were measured. Glycolysis was accelerated, energy reserves fell; alanine rose, citrate fell; finally GABA rose slightly and other metabolites moved toward normal. The authors propose that convulsions result from disordered brain metabolism.

ANIMALS: Rats, Hooded-Lister, M, 90-120 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 70 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Saline

DURATION OF EXPERIMENT: Serial to 150 sec; some rats were allowed to recover

EXAM. TYPE: Behavior, biochemistry

5688

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro

000054955

REFERENCE: Nishie, K., Waiss, A.C., and Keyl, A.C.
Tox. Appl. Pharm. 41:301-307, 1969.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, varying degrees of tremor, opisthotonus and tonic extensor seizures. Authors note higher pH correspond to lower CD_{50} values.

ANIMALS: Mice, albino, M, 20-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: Data reported:
CD_{50} - 38.5 mg/kg I.P., 75 mg/kg P.O.
LD_{50} - 134 mg/kg I.P.,214 mg/kg P.O.

ROUTE AND SITE: I.P., P.O.

CONTROL INFORMATION: Saline or other parameter.

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology.

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro

000054955

REFERENCE: Palfai, T., Kurtz, P. and Gutman, A.
Pharm. Biochem. Behav. 2: 261-262, 1974.

OBSERVED NEUROTOXIC EFFECTS: The compound reduced the brain norepinephrine concentration at 5 but not at 1440 minutes after injection. The time course of induced convulsions and amnesia for memory-task correlated with the brain norepinephrine concentration.

ANIMALS: Mice, M, 70-100 d old, total 84

PREPARATION AND DOSE or HISTORY OF PATIENT: 50 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Distilled water; electric foot-shock.

DURATION OF EXPERIMENT: Serial, 5-1440 min

EXAM. TYPE: Behavior, biochemistry

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro

000054955

REFERENCE: Sequin, J., Fretz, N., Manax, S., Stavrky, G.
Arch. Neurol. 5(3):314-319, 1961.

OBSERVED NEUROTOXIC EFFECTS: CD_{50} 33 mg/kg with isolated twitches of limbs and head, some had clonic convulsions with ventroflexion of head. Convulsant threshold lowered, latent period prolonged and clonic and repeated convulsions more frequent than in control animals. (2) CD_{50} 35 mg/kg.

ANIMALS: Rats, S.D., M, divided into 3 groups.

PREPARATION AND DOSE or HISTORY OF PATIENT: 55 mg/cc stock in saline diluted to .5 cc. Range for estimation of CD_{50} 25, 29, 34, 40 and 47 mg/kg.

ROUTE AND SITE: S.C.

CONTROL INFORMATION: (1) Corpus collusum sectioned under anesthesia
(2) Control, left intact
(3) Sham trepanation.

DURATION OF EXPERIMENT: 5 months

EXAM. TYPE: Behavior

596

COMPOUND: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro

000054955

REFERENCE: Spooner, C.E. and Winters, W.D.
Int. J. Neuropharmacol. 5: 217-236, 1966

OBSERVED NEUROTOXIC EFFECTS: This compound produced different EEG changes according to dose and behavior changes.

ANIMALS: 200 Cockerels, White Leghorn, ages 5-14 d, 45-100 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-100 mg/kg

ROUTE AND SITE: S.C. near axillary vein; I.P. for doses over 0.05 ml

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Behavior, EEG

COMPOUND: Tetrodotoxin
011005699

REFERENCE: Bull, R.J. and Trevor, A.J.
J. Neurochem. 19:999-1009, 1972.

OBSERVED NEUROTOXIC EFFECTS: Inhibited increase of lactate and redistribution of sodium and potassium from electrical stimulation in vitro. Inhibited the influx of calcium in the absence of electrical stimulation.

ANIMALS: Rats, S-D, M, 200-250 g, brain cortex slices in vitro

PREPARATION AND DOSE or HISTORY OF PATIENT: 10^{-7} - 10^{-8} M in incubation medium.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Hours

EXAM. TYPE: Biochemistry

COMPOUND: Tetrodotoxin
011005699

REFERENCE: Koizumi, K., Levine, D.G. and Brooks, C. McC.
Neurology 17:395-404, 1967.

OBSERVED NEUROTOXIC EFFECTS: Depressed spinal monosynaptic and postsynaptic reflexes but not afferent stimuli nor neuromuscular transmission. Motor actions not blocked; cortical evoked potentials less readily depressed.

ANIMALS: Cats

PREPARATION AND DOSE or HISTORY OF PATIENT: "Usually" 1-3 mcg/kg in solution of 10 mcg/ml, one dose. Repeated doses and larger doses are mentioned.

ROUTE AND SITE: I.V. (radial vein) or application to surgically prepared nerves.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior, electrophysiology

COMPOUND: Tetrodotoxin

011005699

REFERENCE: Narahashi, T., Haas, H.G. and Therrien, E.F.
Science 157: 1441-1442, 1967.

OBSERVED NEUROTOXIC EFFECTS: Tetrodotoxin blocks conduction with no change in resting potential. The mechanism of the blockage is similar to that caused by saxitoxin, but recovery of washed axons is slower.

ANIMALS: Lobster (Homarus americanus)

PREPARATION AND DOSE or HISTORY OF PATIENT: Partly isolated giant axons treated with tetrodotoxin at 1×10^{-7} moles/liter.

ROUTE AND SITE: Semi-in vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Up to 100 min

EXAM. TYPE: Electrophysiology

571

COMPOUND: Thallium

REFERENCE: Zook, B.C. and Gilmore, C.E.
J. Am. Vet. Med. Assn. 151(2): 206-217, 1967.

OBSERVED NEUROTOXIC EFFECTS: The animals exhibited depression, vomiting, anorexia, neuropathy and esophageal paralysis. Autopsy revealed scattered neuronal degeneration throughout the cerebrum and cerebellum, and moderate hydrocephalus. Focal axonal degeneration and swelling of the myelin sheaths were observed in the peripheral nervous system.

ANIMALS: 34 dogs, mean age 3 yr (range 6 mo to 8 yr)

PREPARATION AND DOSE or HISTORY OF PATIENT: Presented at clinic with accidental poisoning with thallium-containing compounds.

ROUTE AND SITE: Unknown

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Cases occurred over a 10 yr period

EXAM. TYPE: Behavior, autopsy

572

COMPOUND: Thallium

REFERENCE: Bank, W.J., Pleasure, D.E., Suzuki, K., Nigro, M. and Katz, R. Arch. Neurol. 26:456-463, 1972.

OBSERVED NEUROTOXIC EFFECTS: Axonal degeneration, segmental demyelination, mild peripheral neuropathy, autonomic dysfunction with tachycardia and hypertension. Alopecia.

ANIMALS: Humans: (1)25 yr. old F (2) 27 yr. old M (3) Chronic, 44 yr. old M (4) 7 yr. old M (5) 3 yr. old F

PREPARATION AND DOSE or HISTORY OF PATIENT: (1&2) Unknown (3) Ingestion of rat poison-1 tsp. (4&5) Ingestion of unknown amt. of rat poison

ROUTE AND SITE: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Symptoms cleared after 10 wks for 1&2. (3) 8 wks (4) patient died 78 days after ingestion (5) patient symptoms almost cleared after 30 days.

EXAM. TYPE: Neurologic, urinalysis

COMPOUND: Thallium sulfate

010031591

REFERENCE: Arena, J.M., Watson, G.A. and Sakhadeo, S.S. Clin. Pediat. 4: 267-270, 1965.

OBSERVED NEUROTOXIC EFFECTS: The subject suffered convulsions, stupor, and coma. At autopsy, the brain (1600 g) seemed swollen but no microscopic lesions were identified.

ANIMALS: Human: one M, age 5, 43 lb

PREPARATION AND DOSE or HISTORY OF PATIENT: Exposure to TAT Home Guard Roach Poison, 1% of compound, by playing with empty (?) cans, 6 having been used in home during 2 wk. Urine contained thallium of 20.2 mg/l.

ROUTE AND SITE: Oral and/or dermal

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 2 wk

EXAM. TYPE: Clinical and autopsy

COMPOUND: Thallium sulfate
010031591

REFERENCE: Spencer, P.S., Peterson, E.R., Madrid, R. and Raine, C.S.
J. Cell Biol. 58: 79-95, 1973.

OBSERVED NEUROTOXIC EFFECTS: Mitochondria in axons of peripheral nerve fibers were enlarged after 2 hours, then mitochondria swelled to become axonal vacuoles, which coalesced, and the outer membranes had affinity for thallium which is electron-dense. Swelling made myelin retract from nodes of Ranvier, but there was no degeneration, and conduction was not lost. There were similar changes, but less severe, in dorsal root ganglia and central fibers, but not in other cell types.

ANIMALS: In vitro cross-sections of fetal mouse spinal cord with dorsal root ganglia, 14 d in utero

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5-10 mcg/ml = 1-2 x 10^{-5}M

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: Cultures grown for 12 wk, exposed to thallium for up to 4 d

EXAM. TYPE: Histology

573

COMPOUND: Theobromine, 1-allyl-

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 35.7 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

574

COMPOUND: Theobromine, 1-(2-butenyl)-

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 56.1 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

COMPOUND: Theobromine, 1-ethyl-

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 54.1 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

COMPOUND: Theobromine, 1-(2'-methoxyethyl)-

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 240.0 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

575>

COMPOUND: Theobromine, 1-(2'-methylallyl-)

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 119.0 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

576

COMPOUND: Theobromine, 1-propyl

REFERENCE: Scott, C.C., Anderson, R.C. and Chen, K.K.
J. Pharm. Exp. Ther. 86: 113-119, 1946.

OBSERVED NEUROTOXIC EFFECTS: Produced tetanic convulsions.

ANIMALS: Mice

PREPARATION AND DOSE
or HISTORY OF PATIENT: 96.3 mg/kg (median convulsive dose)

ROUTE AND SITE: I.V., tail vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Clinical

COMPOUND: 4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-
000061336

REFERENCE: Fossieck, B. and Parker, R.H.
J. Clin. Pharm. 14: 504-512, 1974.

OBSERVED NEUROTOXIC EFFECTS: The subject exhibited asterixis and twitching of the limb extremities and the face. The compound found in: cerebrospinal fluid 26 U/ml, cortex 11 and cerebellum 45 U/ml.

ANIMALS: Human: one case, M, 43

PREPARATION AND DOSE
or HISTORY OF PATIENT: Complications following heart surgery, normal EEG, readmission and intensive antibiotics; compound was the 3rd sp. administered: C $\simeq 10^{7}$ units/d

ROUTE AND SITE: Continuous I.V. infusion

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 4 d (patient died)

EXAM. TYPE: Clinical, biochemistry

COMPOUND: 4-Thia-1-azabicyclo(3.2.0) heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(?-phenylacetamido)-
000061336

REFERENCE: Raichle, M.E., Kutt, H., Louis, S. and McDowell, F.
Arch. Neurol. 25:232-239, 1971.

OBSERVED NEUROTOXIC EFFECTS: In 1 human case, encephalopathy followed by recovery on stopping treatment. In cats, 1.3 x 10^6 units/kg produced encephalopathy with myoclonus, more produced status epilepticus and death. In rats, 4.5 x 10^6 units/kg and more produced same, but if anesthetized (ether) only 3 x 10^6 units/kg were needed. Encephalopathy was reversed by penicillinase, i.v. Labeled penicillin was concentrated mainly in membranal-nuclear fraction of homogenates; peak reached 5-10 mins after dose.

ANIMALS: 1 Human patient; 19 adult cats, 2.5-4 kg; 48 Wistar rats, 200-300 g.

PREPARATION AND DOSE
or HISTORY OF PATIENT:
Human: Postsurgery, 10 x 10^6 units 2/d, for 14 d.
Cats: 0.5-1.5 x 10^6 units/kg "or more" repeated in some animals.
Rats: 3-5 x 10^6 units/kg.

ROUTE AND SITE: I.V., by catheter in cats (femoral veins) and rats (jugular).

CONTROL INFORMATION: Human: removal, reinstatement, and again removal of therapy.
Cats and rats: similar techniques, no control groups mentioned.

DURATION OF EXPERIMENT: Minutes to weeks

EXAM. TYPE: Behavior, EEG, biochemistry

577<

COMPOUND: 4-Thia-1-azabicyclo(3.2.0) heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-
000061336

REFERENCE: Tang, A.H. and Schroeder, L.A.
Tox. Appl. Pharm. 12:44-47, 1968.

OBSERVED NEUROTOXIC EFFECTS: Produced little blockade of neuromuscular transmission at doses given.

ANIMALS: 6 Rabbits

PREPARATION AND DOSE
or HISTORY OF PATIENT: 25 mg/kg followed by 50 mg/kg, in saline.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology, behavior

578

COMPOUND: 4-Thia-1-azabicyclo(3.2.0) heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, monopotassium and monosodium salts

REFERENCE: Okada, K., Ayala, G.F. and Sung, J.H.
J. Neuropath. Exp. Neurol. 30(3):337-353, 1971.

OBSERVED NEUROTOXIC EFFECTS: EEG: Periodic cortical paroxysm, ipsilateral only, only with penicillin-G.
Histology: Cortical lesions, progressive with time, similar in 1st and 2nd groups; streptococcal exotoxin caused different lesions, sucrose nil.

ANIMALS: 34 adult cats in 4 groups: 16, 6, 8, 4.

PREPARATION AND DOSE or HISTORY OF PATIENT: Bilateral burr-holes to expose pericruciate gyrus of cortex; topical applications on one side. 1st group received paste as above; 2nd, in Ringer solution (isotonic); 3rd received streptococcal paste or hypertonic sucrose; 4th same plus trypan blue I.V.

ROUTE AND SITE:

CONTROL INFORMATION: The second side was not treated, stated to act as control.

DURATION OF EXPERIMENT: Order of 60-90 min per experiment

EXAM. TYPE: EEG, then histology.

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5726

COMPOUND: 9H-Thieno(3,2-b)(1,4)benzothiazine, 9-acetyl-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

580

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine-4-carboxaldehyde, 6-chloro

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,2-b)(1,4)benzothiazine-9-carboxaldehyde, 7-chloro

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

581

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde, 7- chloro

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5627

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine-4-carboxaldehyde, 6-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,2-b)(1,4)benzothiazine-9-carboxaldehyde, 7-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde, 7(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

583A

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine, 6-chloro-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

584

COMPOUND: 9H-Thieno(3,2-b)(1,4)benzothiazine, 7-chloro-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine, 7-chloro

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine, 7-chloro-4-(3-dimethylaminopropyl)-, hydrochloride

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

585^

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine, 7-chloro-9-(3-dimethylaminopropyl)-, hydrochloride

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

586

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine, 9-(3-dimethylaminopropyl)-, hydrochloride

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine, 4-(3-dimethylaminopropyl)-6-(trifluoromethyl)-, hydrochloride

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4)benzothiazine, 9-(3-dimethylaminopropyl)-7-(trifluoromethyl)-, hydrochloride

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5874

COMPOUND: 4H-Thieno(2,3-b)(1,4)benzothiazine, 6-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5988

COMPOUND: 9H-Thieno(3,2-b)(1,4) benzothiazine, 7-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: 9H-Thieno(3,4-b)(1,4) benzothiazine, 7-(trifluoromethyl)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-(2-amino-4-chlorophenyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5899

COMPOUND: Thiophene, 2-(2-amino-4-chlorophenyl) thio-3-bromo-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

590

COMPOUND: Thiophene, 3-(2-amino-4-chlorophenyl)thio-4-bromo

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-(2-aminophenyl) thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 2-(2-aminophenyl)thio-3-bromo-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

591>

COMPOUND: Thiophene, 3-(2-aminophenyl)thio-4-bromo-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5927

COMPOUND: Thiophene, 3-((2-amino-(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 2-((2-amino-(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-3-bromo-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-((2-amino-(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-4-bromo-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

593<

COMPOUND: Thiophene 3-bromo-2-(4-chloro-2-nitrophenyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

59A

COMPOUND: Thiophene, 3-bromo-4-(4-chloro-2-nitrophenyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-bromo-2-(2-nitrophenyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-bromo-4-(2-nitrophenylthio)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

595

COMPOUND: Thiophene, 3-bromo-2-((2-nitro-(alpha,alpha,alpha-trifluoro-p-tolyl)thio)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

596

COMPOUND: Thiophene, 3-bromo-4-((2-nitro-(alpha,alpha,alpha-trifluoro-p-tolyl)thio)-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene, 3-(4-chloro-2-nitrophenyl) thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiophene hydrazide

REFERENCE: Jenney, E.H. and Pfeiffer, C.C.
J. Pharm. Exp. Ther. 122: 110-123, 1958.

OBSERVED NEUROTOXIC EFFECTS: Convulsions

ANIMALS: Mice, Harlan, 19-21 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.56 mM/kgm

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Acute

EXAM. TYPE: Clinical

597<

COMPOUND:
Thiophene, 3-(2-nitrophenylthio)

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

5982

COMPOUND: Thiophene, 3-(2-nitro-alpha, alpha, alpha-trifluoro-p-tolyl)thio-

REFERENCE: Grol, C.J. and Rollema, H.
J. Med. Chem. 18:857-861, 1975.

OBSERVED NEUROTOXIC EFFECTS: This compound gave positive results in a neurotoxicity screening test in which the criteria were ptosis, sedation and catalepsy.

ANIMALS: Rats and mice, no details

PREPARATION AND DOSE or HISTORY OF PATIENT: 40 mg/kg.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Behavior screening tests

COMPOUND: Thiopyrophosphoric acid, tetrapropyl ester
003244904

REFERENCE: Sherman, H., Ross, E. and Chang, M.T.Y.
Tox. Appl. Pharm. 6:147-153, 1964.

OBSERVED NEUROTOXIC EFFECTS: (1) Convulsions followed in many by death within 18 hr. Survivors were lethargic for 6-19 hr post treatment. (2) 50% cholinesterase inhibition by dose of 380 ppm.

ANIMALS: Cockerels, White Leghorn, single-comb, 10-50/grp, 12 d old

PREPARATION AND DOSE or HISTORY OF PATIENT: (1) Acute: LD_{50} (436.1 mg/kd) in gelatin capsule.
(2) Subacute: 50-800 ppm in feed.

ROUTE AND SITE: Oral

CONTROL INFORMATION: Untreated diet.

DURATION OF EXPERIMENT: 1 wk

EXAM. TYPE: Mortality, behavior, blood ChE

COMPOUND: Thioxanthene-delta(sup) -gamma-propylamine, 2-chloro-N,N-dimethyl, hydrochloride

001229385

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 18 mg/kg

ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

599

COMPOUND: Tin, dioctyl-, acetate

REFERENCE: Robinson, I.M.
Fd. Cosmet. Toxicol. 7: 45-52, 1969.

OBSERVED NEUROTOXIC EFFECTS: Treatment lowered brain epinephrine, norepinephrine and serotonin for 48 hours.

ANIMALS: Rats, Osborne-Mendel, F, 190-220 g, 18/group

PREPARATION AND DOSE or HISTORY OF PATIENT: 800 mg/kg in corn oil

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Equivalent corn oil

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Behavior, biochemistry

600-009

COMPOUND: Tin, triethyl-, sulphate

REFERENCE: Aleu, F.P., Katzman, R. and Terry, R.D.
J. Neuropath. Exp. Neurol. 22(3):403-413, 1963.

OBSERVED NEUROTOXIC EFFECTS: Generalized neuromuscular weakness in hindlimbs and immobilization. Continued injections lead to quadriplegia and death. Severe cerebral edema.

ANIMALS: 21 Rabbits, M, 3 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg/d in saline soln.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 11 rabbits, treatment ns.

DURATION OF EXPERIMENT: Sacr 6-7 d

EXAM. TYPE: Histology, histochemistry, ultrastructural

COMPOUND: Tin, triethyl-, sulphate

REFERENCE: Graham, D.I. and Gonatas, N.K.
Laboratory Investigation 29(6):628-632, 1973.

OBSERVED NEUROTOXIC EFFECTS: Sciatic nerve splitting, nerve fibers underwent Wallerian degeneration. Produced lesions in the peripheral nervous system. Motor dysfunction, spastic paresis of hindlimb. Progressive paraplegia and quadriplegia. Swollen and edamatous brains. Myelin splitting.

ANIMALS: 12 Rats, Osbourne-Mendell, M and F, (6) 3 mo. old and (6) 12 mo. old.

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mg/l in drinking water

ROUTE AND SITE: Oral

CONTROL INFORMATION: 12 matched for age and sex.

DURATION OF EXPERIMENT: Sacr by 22nd

EXAM. TYPE: Ultrastructural, clinical, histology

COMPOUND: Tin, triethyl-, sulphate

REFERENCE: Katzman, R. Aleu, F. and Wilson, C.
Arch. Neurol. 9:178-187, 1963.

OBSERVED NEUROTOXIC EFFECTS: Water content of white-matter (dry-matter basis) rose by 91%; no change in Na-Mg-dependent ATPase; this, other chemistry, and histology indicated that edema fluid was located in intramyelinic vacuoles.

ANIMALS: 40 rabbits, white, M, 2-3 kg.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1 mg/kg in saline.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 20 untreated controls.

DURATION OF EXPERIMENT: Up to 7 hr.

EXAM. TYPE: Biochemistry, histology

601<

COMPOUND: Tin, triethyl-, sulphate

REFERENCE: Suzuki, K.
Exp. Neurol. 31:207-213, 1971.

OBSERVED NEUROTOXIC EFFECTS: All acute rats died in 3 d, hemorrhagic encephalopathy. Chronic rats no behavior signs but spongy degeneration found throughout the central nervous system white-matter.

ANIMALS: Rats, Wistar Acute: 20 newborn, 10 eight d old, 2 two mo. old.
Chronic: 8 newborn, their dam, 2 two mo. old.

PREPARATION AND DOSE or HISTORY OF PATIENT: Acute: 5 mg/kg/d for 3 d.
Chronic: 5 mg/l in water for 4 mo.

ROUTE AND SITE: Acute: I.P. Chronic: Oral

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 3 d and 4 mo.

EXAM. TYPE: Histology and behavior

602 209

COMPOUND: Tin, trioctyl-, dilaurate

REFERENCE: Robinson, I.M.
Fd. Cosmet. Toxicol. 7: 45-52, 1969

OBSERVED NEUROTOXIC EFFECTS: Treatment lowered brain epinephrine, norepinephrine and serotonin for 48 hours.

ANIMALS: Rats, Osborne-Mendel, F, 190-220 g, 18/group

PREPARATION AND DOSE or HISTORY OF PATIENT: 800 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Equivalent corn oil

DURATION OF EXPERIMENT: Serial to 48 hr

EXAM. TYPE: Behavior, biochemistry

COMPOUND: p-Toluamide, N-isopropyl-alpha-(2-methylhydrazino)

000671169

REFERENCE: Chaube, S. and Murphy, M.L.
Teratology 2: 23-32, 1969.

OBSERVED NEUROTOXIC EFFECTS: Exencaphaly, encephalocele, and acephaly, seen after treatment on d 9 only, after doses of 1/2 to 1/45 of the female lethal dose of 550 mg/kg.

ANIMALS: Rats, CF Wistar, F in estrus, 200-250 g, total 275

PREPARATION AND DOSE or HISTORY OF PATIENT: 5-550 mg/kg in 0.85% NaCl, one dose on 5-17th d of gestation.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: 23 controls vehicle only.

DURATION OF EXPERIMENT: Sacr 21d

EXAM. TYPE: Histology of fetuses

COMPOUND: p-Toluamide, N-isopropyl-alpha-(2-methylhydrazino)-

000671169

REFERENCE: Herman, E.H., Lee, I.
Toxicol. Appl. Pharmacol. 22:484-496, 1972.

OBSERVED NEUROTOXIC EFFECTS: Central nervous system depression observed in anesthetized and unanesthetized animals. (1) Anesthetized monkeys showed decrease in EEG activity. (2) Unanesthetized animals given similar doses induced somnolence with concurrent synchronization of the EEG pattern, producing ataxia.

ANIMALS: Monkeys, M, 3.5-4.5 kg (1) 12 (2) 3 (3) 15 animals

PREPARATION AND DOSE
or HISTORY OF PATIENT: (1) Anesthetized: d 25, 50, 100, 200 or 400 mg/kg in saline.
(2) Unanesthetized: 100 mg/kg, preceded 15 min by dl-propanolol or d-propanolol 0.5 mg/kg.
(3) Unanesthetized: 25, 50, 200, 400 mg/kg. (3 animals per dose)

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 60 mins.

EXAM. TYPE: Electroencephalography, electrocardiography

603>

COMPOUND: Toluene

000108883

REFERENCE: Grabski, D.A.
Am. J. Psychiat. 118: 461-426, 1961.

OBSERVED NEUROTOXIC EFFECTS: The subject showed a gait characteristic of cerebellar damage, intention tremor of the hands and feet, and rebound phenomena in all limbs. There was no abnormality of olfaction, vision, orientation, memory, mentation, or of cranial nerves 5,7,9,11,12 or of posterior column signs, toe position or vibratory sense. The author inferred irreversible cerebellar damage, probably to the lateral lobes.

ANIMALS: Human, 1 case, M, 19 at start

PREPARATION AND DOSE
or HISTORY OF PATIENT: Addictive pattern of self administration over 6 yr

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 6 yr

EXAM. TYPE: Behavior, clinical, neurological

604

COMPOUND: Toluene

000108883

REFERENCE: Knox, J.W. and Nelson, J.R.
New Eng. J. Med. 275: 1494-1496, 1966.

OBSERVED NEUROTOXIC EFFECTS: Ataxia, tremors, emotional lability, right Babinski sign, diffuse EEG slowing, diffuse cerebral atrophy by pneumoencephalography, interpreted as permanent brain damage.

ANIMALS: Human: 1 case, M, 33

PREPARATION AND DOSE or HISTORY OF PATIENT: History of glue- or pure toluene-sniffing for 14 yr with exposure estimated at about 1 gallon/mo; minimal alcohol consumption, one episode of carbon tetrachloride intoxication, frequent admissions to mental hospitals.

ROUTE AND SITE: Inhalation

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 14 yr

EXAM. TYPE: Behavioral, EEG, pneumoencephalography

COMPOUND: Triethylcholine

REFERENCE: Hartung, R. and Cornish, H.H.
Tox. Appl. Pharm. 12:486-494, 1968.

OBSERVED NEUROTOXIC EFFECTS: This compound was tested with a group of other aminoethanols and choline analogs, all of which inhibited cholinesterase in vitro. In vitro inhibition increases as the number of carbon atoms attached on the nitrogenous head of the 2-aminoethanol molecule. In the in vivo tests the oral LD_{50}'s were uniformly higher than the i.p. LD_{50} values.

ANIMALS: Rats, S-D, M

PREPARATION AND DOSE or HISTORY OF PATIENT: In vitro: 10^{-4} to 10^{-1}.
In vivo: LD_{50} and lower doses.

ROUTE AND SITE: Oral, i.p., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry

COMPOUND: 1-alpha-H,5-alpha-H-tropane-2-beta-carboxylic acid, 3-beta-hydroxy-methyl ester, benzoate (ester) hydrochloride
000053214

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: The compound enhanced the effect of Yohimbine and lowered its lethal dosage.

ANIMALS: Mice, TT, M, 18-25 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: ED_{50} 15 mg/kg
ED_{50} = dose producing a 50% mortality of mice injected S.C. with yohimbine hydrochloride (20 mg/kg).

ROUTE AND SITE: S.C., Oral

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

605

COMPOUND: 1-alpha-H,5-alpha-H-tropane, 3-alpha-(diphenyl methoxy)

REFERENCE: Pfeiffer, C.C., Murphree, H.B., Jenney, E.H., Robertson, M.C., Randall, A.H. and Bryan, L.
Neurology 9: 249-250, 1959.

OBSERVED NEUROTOXIC EFFECTS: The authors concluded that synthetic atropines are more active hallucinogens than atropine or scopolamine, producing effects lasting 24-48 hr. Synthetic antitremor drugs had fewer peripheral nervous system side-effects, but central nervous system side-effects (hallucinations) may have been exaggerated.

ANIMALS: Human: prison volunteers, drug-sophisticated, no other details

PREPARATION AND DOSE or HISTORY OF PATIENT: 2 mg/man

ROUTE AND SITE: Oral

CONTROL INFORMATION: LSD-25: 0, 25, 50, 100 mcg/man

DURATION OF EXPERIMENT: Up to 3 d

EXAM. TYPE: Opinion of volunteers

COMPOUND: Tropanium, 3-alpha-hydroxy-9-methyl, p-tolylacetate

REFERENCE: Friess, S.L. and Anderson, J.B.
Tox. Appl. Pharm. 22: 208-212, 1972.

OBSERVED NEUROTOXIC EFFECTS: With tropine-p-tolylacetate or its quaternary methiodide separately, there was reversibility of induced blockade on washing depending on the extent of N-substitution, quaternary methiodide being more reversible than the tertiary ester. But 1 mM of tropine-p-tolylacetate added to 5mM of its quaternary methiodide halved the reversibility of quaternary methiodide blockade. More than 1 mM of tropine-p-tolylacetate had no more effect.

ANIMALS: In vitro excitable nodes of Ranvier in single fibers of frog sciatic nerve.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 5mM for separate incubations with tropine-p-tolylacetate and its quaternary methiodide; tropine-p-tolylacetate:the quaternary methiodide ratios in mixed incubations 1:5, 2:5, and 3:5 in mM.

ROUTE AND SITE: In vitro

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Incubation, removal, washing, observing by electrophysiology

COMPOUND: Tropanol aryl esters, (unspecified)

REFERENCE: Friess, S.L., Durant, R.C., Baldridge, H.D. and Reber, L.J.
Tox. Appl. Pharm. 7:694-707, 1965.

OBSERVED NEUROTOXIC EFFECTS: Stereospecific effects obtained at synaptic chemoreceptors, features of intoxication syndrome, interpreted in terms of chemical configuration of receptor sites.

ANIMALS: Rats: Long-Evans, M: in vivo and phrenic nerve-diaphragm preparations.
Cats: In situ denervated gastrocnemius-soleus preparations
Frogs: In vitro, nodes of Ranvier in single fibers of sciatic nerve.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10^{-4} to 10^{-3} M; in some tests 10^{-7} to 5×10^{-1} M.

ROUTE AND SITE: Prepared

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

COMPOUND: Tropine, and aryl esters (unspecified)

REFERENCE: Reber, L.J., Allen, C.H., Durant, R.C. and Friess, S.L.
Tox. Appl. Pharm. 5: 625-636, 1963.

OBSERVED NEUROTOXIC EFFECTS: Convulsions, paralysis (i.v.), dose-related. In vitro potentiation of evoked twitch responses, interpreted in terms of chemoreceptor structure-activity relationships.

ANIMALS: Mice, white, M, 18-22 g, 10/group
Rat phrenic nerve-diaphragm preparations
Cats, no details

PREPARATION AND DOSE
or HISTORY OF PATIENT: Two new esters were synthesized, described structurally.
I-ϕ-HCl, mice 32.7 mg/kg (LD_{50}), cats 10-25.5 mg/kg (dose)
II-ϕ-HCl, mice 35 mg/kg (LD_{50}), cats 25 mg/kg (dose)
Rat PD-prep: 10^{-4} to > 5 x 10^{-3} M in medium

ROUTE AND SITE: I.V., in vitro

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: ns

EXAM. TYPE: Biochemistry, electrophysiology

607<

COMPOUND: 2-d-Tropine, p-nitrophenylacetate, (ester)

REFERENCE: Friess, S.L., Baldridge, H.D., Durant, R.C. and Reber, L.J.
Tox. Appl. Pharm. 7:794-803, 1965.

OBSERVED NEUROTOXIC EFFECTS: Behaviorally and electrically less toxic than the 3-tropanyl isomers; interpreted in terms of chemical configuration of synaptic receptor sites.

ANIMALS: Mice, NMRI, intact
Cats, mongrel, intact and denervated gastronemius muscle preparation
Rats, in vitro phrenic nerve-diaphragm preparations

PREPARATION AND DOSE
or HISTORY OF PATIENT: Mice: LD_{50} (23-63 mg/kg)
Cats: 30-45 mg/kg
In vitro: 10^{-5} to 10^{-3} M

ROUTE AND SITE: I.V., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology

608

COMPOUND: 2-alpha-Tropine, p-tolylacetate, (ester)

REFERENCE: Friess, S.L., Baldridge, H.D., Durant, R.C. and Reber, L.J.
Tox. Appl. Pharm. 7:794-803, 1965.

OBSERVED NEUROTOXIC EFFECTS: Behaviorally and electrically less toxic than the 3-tropanyl isomers; interpreted in terms of chemical configuration of synaptic receptor sites.

ANIMALS: Mice, NMRI, intact
Cats, mongrel, intact and denervated gastronemius muscle preparations
Rat, in vitro phrenic nerve-diaphragm preparations

PREPARATION AND DOSE or HISTORY OF PATIENT: Mice: LD_{50} (23-63 mg/kg)
Cats: 30-45 mg/kg
In vitro: 10^{-5} to 10^{-3} M

ROUTE AND SITE: I.V., in vitro

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiology.

COMPOUND: Turpentine

REFERENCE: Sperling, F., Marcus, W.L. and Collins, C.
Tox. Appl. Pharm. 10:8-20, 1967.

OBSERVED NEUROTOXIC EFFECTS: LC_{50} for rats, 1-6 hr exposures, were 12-20 mg/liter; 2-hr LC_{50} for mice was 29 mg/liter; highest concentration was in brain. Ataxia, tremors, convulsions produced by I.V., sometimes by inhalation.

ANIMALS: Rats, Wistar, M, 140-200 g
Mice, Groups of 10, Swiss-Webster, M, 25-30 g

PREPARATION AND DOSE or HISTORY OF PATIENT: Vapors generated at 25-27°, various concentrations to measure LC_{50} for 1-6 hr. LD_{50} for I.V. in mice.

ROUTE AND SITE: Inhalation, I.V.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Clinical, polygraph, biochemistry

COMPOUND: o-Tyrosine, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Neurochem. 6:117-141, 1960.

OBSERVED NEUROTOXIC EFFECTS: Treatment caused excitation or depression of neuronal activity. Excitatory ranking: glutamic, β-aminoglutaric, aspartic, cysteic, cysteine-sulfinic acids, β-hydroxyglutamic, N-methylaspartic, N-formiminoaspartic acids.
Depressant ranking: β-alanine, GABA, taurine, N-methyl-β-alanine, δ-amino-β-hydroxybutyric, glycine, α-alanine, δ-aminovaleric, β-aminoisobutyric acids.
Structure-activity relationships established.

ANIMALS: Cats, surgically prepared to exposed motoneurones, Renshaw cells or dorsal horn interneurones in lumbar cord.

PREPARATION AND DOSE or HISTORY OF PATIENT: Qualitative doses.

ROUTE AND SITE: Topical, iontophoresis

CONTROL INFORMATION: Laboratory

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemistry, electrophysiology

609>

COMPOUND: Uracil, 5-fluoro

000051218

REFERENCE: Koenig, H. and Patel, A.
Trans. Amer. Neurol. Assoc. 94:290-292, 1969.

OBSERVED NEUROTOXIC EFFECTS: Neuronal and glial lesions in cerebellar and vestibular structures, onset of cerebellar ataxia and convulsions caused by formation of fluoroacetate with consequent blockage of the Krebs cycle.

ANIMALS: Cats

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.5-30 mg/kg

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Biochemical, histological

610

COMPOUND: Uracil, 5-fluoro

000051218

REFERENCE: Koenig, H. and Patel, A.
Arch. Neurol. 23:155-160, 1970.

OBSERVED NEUROTOXIC EFFECTS: Citrate in brain elevated. In 2 patients, citrate in whole blood was elevated. Interpreted as inhibition of citrate-isocitrate step of Krebs cycle (aconitase-catalyzed). Fluorouracil thought metabolized to fluoracetate. Return to normal 5 d after treatment.

ANIMALS: 24 Cats, adult, M and F, 2-3 kg. 2 Human patients.

PREPARATION AND DOSE or HISTORY OF PATIENT: 7.5-30 mg/kg i.v. or 20 mg/kg i.p. Also α-fluoro-β-alanine 5-10 mg/kg i.p., and fluoroacetate 0.1-0.4 mg/kg. Patients 15 mg/kg/d for 5 d, or 7.5 mg/2 d.

ROUTE AND SITE: I.V. or I.P. Human: I.V.

CONTROL INFORMATION: Saline controls.

DURATION OF EXPERIMENT: Serial sacr to 48 hr.

EXAM. TYPE: Biochemical

COMPOUND: Uracil, 5-fluoro

000051218

REFERENCE: Kury, G. and Craig, J.M.
Arch. Path. 81: 166-173, 1966.

OBSERVED NEUROTOXIC EFFECTS: Exencephaly with severe brain malformations, neuraxis with necrotic neuroblasts. Some microphthalmia and necrotic neurons in neuraxis.

ANIMALS: Eggs, White Leghorn, fertilized

PREPARATION AND DOSE or HISTORY OF PATIENT: Teratogenic dosage schedules, from d 1 to d 4

ROUTE AND SITE: Inoculation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 21 d

EXAM. TYPE: Teratological

COMPOUND: Uracil, 5-fluoro

000051218

REFERENCE: Riehl, J-L., and Brown, W.J.
Neurology 14: 961-967, 1964.

OBSERVED NEUROTOXIC EFFECTS: Acute cerebellar syndrome seen in humans, reversed on stopping or lowering dosage of compound; autopsies showed chromatolysis of neurons of olivary and dentate nuclei, and sparse cells in granular layer of cerebellum. Cats showed multifocal edema and destruction of Purkinje cells and granular layer of cerebellum; myelin and axons were affected.

ANIMALS: Human: 4 cases, 46-69, and 2 autopsies
Cats: 3 healthy, 3-3.5 kg

PREPARATION AND DOSE or HISTORY OF PATIENT: Humans: Up to 15 mg/kg/d, subsequently lowered
Cats: 15 mg/kg/d

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: Humans: various. Cats: to 7 d

EXAM. TYPE: Behavior, histology

611<

COMPOUND: Urea, ((p-bromophenyl)acetyl)-

30241862

REFERENCE: Chen, F.C.K. and Cavenagh, J.B.
Br. J. Exp. Path. 52:315-321, 1971.

OBSERVED NEUROTOXIC EFFECTS: Liver damage studies indicated that substance was neurotoxic per se; adults over 9-10 wk old more susceptible than juveniles, no sex differences. Substance was probably detoxified by liver but not by microsomal enzymes induced by barbiturates. Paresis in limbs dose-related.

ANIMALS: Rats, Porton, M and F, 180-250 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 50-400 mg/kg/d for 2 d.
Rats prepared in various ways with neurotoxic treatments.

ROUTE AND SITE: Gavage

CONTROL INFORMATION: 28 healthy rats.

DURATION OF EXPERIMENT: 2 wk

EXAM. TYPE: Behavior, enzyme determinations.

612<

COMPOUND: Urea, ((p-bromophenyl)acetyl)-

30241862

REFERENCE: Blakemore, W.F. and Cavanagh, J.B.
Brain 92:789-804, 1969.

OBSERVED NEUROTOXIC EFFECTS: "Neuroaxonal dystrophy" in "dying back" process from second wk, persisting for at least 10 wk after treatment.

ANIMALS: Rats, SPF, M, about 200 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 200 mg/kg/d in DMSO.

ROUTE AND SITE: Oral, via cannula

CONTROL INFORMATION: DMSO only, number ns.

DURATION OF EXPERIMENT: Serial sacr 5 d to 10 wk.

EXAM. TYPE: Histology

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Cravioto, H., Weiss, J.F., Weiss E. de C., Goebel, H.H. and Ransohoff, J.
J. Acta Neuropath. 23:265-280, 1973.

OBSERVED NEUROTOXIC EFFECTS: Peripheral nervous system tumors in 80%, Central nervous system in 16% of treated rats. Mostly trigeminal nerve in peripheral nerves: Schwann cells behaving as if malignant. Transplants, direct or cultured, behaved similarly, similar cell composition.

ANIMALS: Rats, 10 CFE and 6 inbred BD-IX, F

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mg/kg in last 5 d of gestation. Tumors cultured and transplanted.

ROUTE AND SITE: I.V., Transplants intracerebral or i.p., or s.c.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Cytology, electronmicroscopy

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Fornatto, L. and Schiffer, D.
Acta Neuropath. 20:199-206, 1972.

OBSERVED NEUROTOXIC EFFECTS: Five neurinomas were produced. Abundant spindle cells, mitoses, necroses, and cysts; signs of high invasiveness. Activities of acid phosphatase, β-glucuronidase, lysosomes, and pinocytosis were characterized.

ANIMALS: Rats, Long-Evans, newborn

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50 mg/kg.
Five neurinomas of the Vth cranial nerve cultured in vitro, with 4-30 particle explanatations each.

ROUTE AND SITE: Intracerebral; s.c.

CONTROL INFORMATION: 2 Human neurinomas of the VIIIth cranial nerve with 28 particle explanations.

DURATION OF EXPERIMENT: 20 d of culture followed by histochemistry

EXAM. TYPE: Histology, histochemistry

613<

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Grossi-Paoletti, E., Paoletti, P., Schiffer, D. and Fabiani, A.
J. Neurol. Sci. 11:573-581, 1970.

OBSERVED NEUROTOXIC EFFECTS: Tumors in 41 (89%) offspring, total 58: 40 intracranial, 18 spinal. Types: 35 neurinomas, 20 oligodendrogliomas, 2 ependymomas, 1 glioblastoma.

ANIMALS: Rats, Long-Evans, F at d 17 of pregancy: 46 young.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 10 mg/kg one dose on d 17 of pregnancy.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 150-400 d

EXAM. TYPE: Autopsy, histology

614

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Jones, E.L., Searle, C.E. and Smith, W.T.
J. Path. 109:123-139, 1973.

OBSERVED NEUROTOXIC EFFECTS: 33 Of 34 had 71 tumors; 62 cranial, 9 spinal.

ANIMALS: Rats, Wistar and hooded-Norway, newborn, total 38; 34 survived weaning.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.02 ml/rat 24 hr after birth (10 mg/kg).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 191-680 d sacr when neuropathology seen.

EXAM. TYPE: Histology, pathology

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Lantos, P.L.
J. Path. 116:107-115, 1975.

OBSERVED NEUROTOXIC EFFECTS: 39 of 40 offspring developed either gliomas or malignant schwannomas. Ultrastructure of resultant macrophages is reported.

ANIMALS: 9 rats, BD-IX, F, pregnant d 15

PREPARATION AND DOSE
or HISTORY OF PATIENT: 30 mg/kg one dose in citrate buffer

ROUTE AND SITE: I.V.

CONTROL INFORMATION: 2 rats buffer only.

DURATION OF EXPERIMENT: 160-300 d

EXAM. TYPE: Histology

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Pfaffenroth, M.J., Das, G.D. and McAllister, J.F. Teratology 9:305-316, 1974.

OBSERVED NEUROTOXIC EFFECTS: Microencephaly, especially of cortex and cerebellum. The earlier the injection, the greater the decrease. No recovery in adulthood. At 4 mo. some brain tumors observed.

ANIMALS: Rats, Wistar, F, pregnant

PREPARATION AND DOSE or HISTORY OF PATIENT: 60 mg/kg/d on d 14-21 of gestation in saline at pH 4.5.

ROUTE AND SITE: I.V., tail

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Progeny killed 0-75 d after birth (7 groups, 2/gp); some observed for 4 mo.

EXAM. TYPE: Macroscopical (histology to be reported elsewhere)

615>

COMPOUND: Urea, ethyl nitroso-

000759739

REFERENCE: Wechsler, W., Pfeiffer, S.E., Swenberg, J.A. and Koestner, A. Acta Neuropath. 24: 287-303, 1973.

OBSERVED NEUROTOXIC EFFECTS: 18 brain tumors, 1 cord tumor and 22 peripheral nervous system tumors were studied. S-100 protein isolated from 16 central nervous system and 21 peripheral nervous system tumors, but found in only 1/10 non-neurogenic tumors. Authors claim that S-100 protein is "definitive indication" of nerve cell participation in a tumor.

ANIMALS: Rats, CD, CDF, or BDIX, pregnant F, 3rd period gestation.

PREPARATION AND DOSE or HISTORY OF PATIENT: 1, 5, 20 or 50 mg/kg to produce tumors in offspring.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology, biochemistry.

616

COMPOUND: Urea, hydroxy-

000127071

REFERENCE: Ferm, V.H.
Arch. Path. 81: 174-177, 1966.

OBSERVED NEUROTOXIC EFFECTS: Exencephaly and failure of neural tube to close after administration of compound, more so after i.v. treatment.

ANIMALS: Golden hamsters, F, pregnant, 100-125 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 50 mg/hamster on d 9, 10, 11 or 12

ROUTE AND SITE: I.V. lingual vein

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 24-72 hr. after treatment.

EXAM. TYPE: Teratological

COMPOUND: Urea, methyl nitroso-

000684935

REFERENCE: Schiffer, D., Fabiani, A., Grossi-Paoletti, E. and Paoletti, P. J. Neurol. Sci. 11:559-572, 1970.

OBSERVED NEUROTOXIC EFFECTS: 29 (80%) rats developed central nervous system tumors: total of 46 intracranial and 8 cord tumors. Cranial mostly oligodendrogliomas and other gliomas. Cord: 6 gliomas, 2 neurinomas.

ANIMALS: 36 Rats, Long-Evans; M, aged 1-2 mo.

PREPARATION AND DOSE
or HISTORY OF PATIENT: 25 mg/kg/mo (one dose/mo.) for 8 mo.

ROUTE AND SITE: I.V. tail vein

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: 8 mo.

EXAM. TYPE: Clinical, histology

COMPOUND: Urea, methyl nitroso-

000684935

REFERENCE: Wechsler, W., Pfeiffer, S.E., Swenberg, J.A. and Koestner, A. Acta Neuropath. 24: 287-303, 1973.

OBSERVED NEUROTOXIC EFFECTS: 18 brain tumors, 1 cord tumor and 22 peripheral nervous system tumors were studied. S-100 protein isolated from 16 central nervous system and 21 peripheral nervous system tumors, but found in only 1/10 non-neurogenic tumors. Authors claim that S-100 protein is "definitive indication" of nerve cell participation in a tumor.

ANIMALS: (1) Rats, Charles River, adult, CD and CDF (all SPF)

PREPARATION AND DOSE or HISTORY OF PATIENT: 180 mg/kg as 5 mg/kg/wk, carcinogenic dose

ROUTE AND SITE: Oral, i.p., i.v., or s.c.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Histology, biochemistry

617>

COMPOUND: Urea, (2-phenylbutyryl)-

000090493

REFERENCE: Orloff, M.J., Feldman, P.E., Shaiova, C.H. and Pfeiffer, C.C. Neurology 1: 377-385, 1951.

OBSERVED NEUROTOXIC EFFECTS: Doses used to control grand mal seizures produced "extreme toxicity": cramps, anorexia, dizziness, ataxia, disorientation, athetoid movements. The effects were not persistent.

ANIMALS: Humans: 10 institutionalized epileptics

PREPARATION AND DOSE or HISTORY OF PATIENT: Humans: 1.2-7.2 g/patient/d with other drugs, various periods

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: 4-64 d

EXAM. TYPE: Clinical

618

COMPOUND: Urease

REFERENCE: Gibson, G.E., Zimber, A., Krook, L., Richardson, E.P., Visek, W.J. J. Neuropath. and Exper. Neurol. 33(2):201-211, 1974.

OBSERVED NEUROTOXIC EFFECTS: Brain tissue examined 30-38 hr after injection showed increases in size and number of astrocytic nuclei; the astrocytes were typical in appearance of Alzheimer II cells. Spongy vacuolation of neurophil. Behavioral changes included coma with or without generalized convulsive seizures.

ANIMALS: Mice, S.W., M, 18-21 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 0.2 ml of crystalline jackbean urease injected twice with 0.4 units of urease per mouse. Others received 55 units/kg body wt. - LD_{50}.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Injected with .85% NaCl.

DURATION OF EXPERIMENT: Approx. 36 hrs after injection depending on behavior conditions.

EXAM. TYPE: Histological

COMPOUND: Uridine, 2'-deoxy-5-fluoro

REFERENCE: Kury, G. and Craig, J.M. Arch. Path. 81: 166-173, 1966.

OBSERVED NEUROTOXIC EFFECTS: Exencephaly with severe brain malformations, neuraxis with necrotic neuroblasts, no abnormalities of cord and autonomic ganglia.

ANIMALS: Eggs, White Leghorn, fertilized

PREPARATION AND DOSE or HISTORY OF PATIENT: Teratogenic dosage schedules, from d 1 to d 4

ROUTE AND SITE: Inoculation

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 21 d

EXAM. TYPE: Teratological

COMPOUND: Uridine, 2'-deoxy-5-fluoro

REFERENCE: Maruyama, S., Chiga, M. and D'Agostino, A.N.
J. Neuropath. Exp. Neurol. 27:96-107, 1968.

OBSERVED NEUROTOXIC EFFECTS: Necrosis in central nervous system progressive from 3 hr. In cord dorsal columns and horns, in brain the telencephalon, hippocampi, and corpus callosum were most affected. Interpreted as selective effects on cells in S phase in presence of DNA inhibition.

ANIMALS: 22 Rats, S-D, pregnant F, about 300 g.

PREPARATION AND DOSE or HISTORY OF PATIENT: 60 mg in water (average 200 mg/kg). Histolog, on 5 fetuses per litter.

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Fetuses from 1 rat/d on days 13, 14, 15 and 17.

DURATION OF EXPERIMENT: Serial sacr 30 min to 4 d.

EXAM. TYPE: Histology

619

COMPOUND: Valeric acid, 2-amino-5-sulfo-, DL-

REFERENCE: Curtis, D.R. and Watkins, J.C.
J. Physiol. 166:1-14, 1963.

OBSERVED NEUROTOXIC EFFECTS: N-methyl-D-aspartic and D-homocysteic acids were stronger excitants of depolarization than all others. With some compounds the action was prolonged for many seconds after the stimulus was terminated, notably N-n-propyl-D-aspartic acid. There were no differences among types of neurons tested; structure-activity relationship was observed.

ANIMALS: Cats prepared for electrophoretic application of chemicals to single central nervous system neurons.

PREPARATION AND DOSE or HISTORY OF PATIENT: Dilutions 0.1-0.5 M of 31 compounds mainly of aspartic, glutamic and cysteic acids listed in order of potency of results.

ROUTE AND SITE: Electrophoretic application, various sites in central nervous system.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: ns.

EXAM. TYPE: Electrophysiological

620

COMPOUND: Valeric acid, 2,2-diphenyl-, 2-(diethylamino) ethyl ester

REFERENCE: Gaitonde, B.B. and Borison, H.L.
Tox. Appl. Pharm. 8:118-125, 1966.

OBSERVED NEUROTOXIC EFFECTS: 25 mg/kg cause clonic convulsions; repeated doses i.p. cumulative, causing anorexia, convulsions and death. Intracarotid doses stimulated forebrain; doses into vertebral artery depressed respiratory center in lower brainstem. Peripheral nervous system effects as well.

ANIMALS: Cats, no details, some surgically prepared.

PREPARATION AND DOSE or HISTORY OF PATIENT: 2-25 mg/kg i.v. or intracarotid, or in vertebral artery; 10 or 40 mg/kg intraportal; 25-200 mg/kg i.p.

ROUTE AND SITE: I.V. or intracarotid, intraportal, i.p.

CONTROL INFORMATION: ns.

DURATION OF EXPERIMENT: Various time schedules.

EXAM. TYPE: Clinical, physiograph, autopsy

COMPOUND: Veratrum alkaloids (Unspecified)

REFERENCE: Kolb, E.J. and Korein, J.
Neurology 11: 159-163, 1961

OBSERVED NEUROTOXIC EFFECTS: In 3 cases, produced reversible episodic myotonic syndrome, dose-related intensity; in one case episodic peripheral neuropathy.

ANIMALS: Human: 4 patients, M, with hypertension

PREPARATION AND DOSE or HISTORY OF PATIENT: Up to 1 mg 3 times/d

ROUTE AND SITE: Oral

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: Months

EXAM. TYPE: Clinical

COMPOUND: Vincaleukoblastine
000865214

REFERENCE: Gottschalk, P.G., Dyck, P.J. and Kiely, J.M.
Neurol. 18: 875-882, 1968.

OBSERVED NEUROTOXIC EFFECTS: Generalized weakness, numbness of toes, decreased muscle stretch reflexes. Death occured four weeks after end of treatment. Sural nerves contained unusually large fibers, and other signs of Wallerian degeneration were found.

ANIMALS: 1 Human, F, age 46 yr

PREPARATION AND DOSE
or HISTORY OF PATIENT: 80 mg in 8 wk

ROUTE AND SITE: I.V.

CONTROL INFORMATION: Group of rats, not described

DURATION OF EXPERIMENT: 8 wk

EXAM. TYPE: Histology

621>

COMPOUND: Vincaleukoblastine, sulfate (1:1) (salt)
000143679

REFERENCE: Smith, B.
J. Neurol. Neurosurg. Psychiat. 30: 506-510, 1967.

OBSERVED NEUROTOXIC EFFECTS: The myenteric plexus was examined, and histological changes were found.

ANIMALS: 45 Mice, TO, CFW and Porton strains, 20-25 g

PREPARATION AND DOSE
or HISTORY OF PATIENT: 0.005 or 0.05 mg/d for 3-6 d, 18 mice
Acute study: 10 mg I.P. or 2 mg I.V. one dose

ROUTE AND SITE: I.P.

CONTROL INFORMATION: ns

DURATION OF EXPERIMENT: 2 d to 3 mo after last dose. Acute: 20 min.

EXAM. TYPE: Histology

629

COMPOUND: Xylitol

REFERENCE: Evans, GW., Phillips, G., Mukherjee, T.M., Snow, M.R., Lawrence, J.R. and Thomas, D.W.
J. Clin. Path. 26: 32-36, 1973

OBSERVED NEUROTOXIC EFFECTS: Calcium oxalate crystals deposited in midbrain, almost certainly as indirect result of xylitol.

ANIMALS: Human: 1 M, 58

PREPARATION AND DOSE or HISTORY OF PATIENT: Kidney transplant 3 mo earlier; acute pancreatitis, severe hypertension, epigastric mass. 3 infusions of cpd, followed by 2 dialyses. Total dose: 1000 ml of 25% and 500 ml of 50% solutions.

ROUTE AND SITE: I.V.

CONTROL INFORMATION: None

DURATION OF EXPERIMENT: About 2 wk

EXAM. TYPE: Autopsy, histology of midbrain sections

COMPOUND: Yohimbam-16-alpha-carboxylic acid, 17-alpha-hydroxy-, methyl ester
000146485

REFERENCE: Quinton, R.M.
Br. J. Pharmac. 21:51-66, 1963.

OBSERVED NEUROTOXIC EFFECTS: Treatment produced ptosis, sedation, prostration, and clonic, but never tonic, convulsions. It also decreased brain norepinephrine, but had no effect on monoamine oxidase activity.

ANIMALS: Mice, TT, M, 18-25 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 20 mg/kg and up to LD_{50} (43.9 mg/kg).

ROUTE AND SITE: S.C.

CONTROL INFORMATION: Various

DURATION OF EXPERIMENT: Various

EXAM. TYPE: Behavior, electrophysiology, biochemistry

COMPOUND: 3-beta,20-alpha-Yohimban-16-beta-carboxylic acid, 18-beta-hydroxy-11,17-alpha-dimethoxy-, methyl ester, 3,4,5-trimethoxybenzoate (ester)

000050555

REFERENCE: Young, R.L., Albano, R.F., Charnecki, A.M., Opar, G.E. and Sheppard, H.
Res. Comm. Chem. Path. Pharm. 5(2):237-286, 1973.

OBSERVED NEUROTOXIC EFFECTS: Treated mice were cataleptic; neuraxis contained defects of phospho-creatine and ATP metabolism, differing according to thermic conditions. The authors concluded that reserpine affects high-energy phosphate compounds of the brain and interacts with temperature-regulation.

ANIMALS: Mice, CF-IS, M, 17-23 g

PREPARATION AND DOSE or HISTORY OF PATIENT: 5 mg/kg

ROUTE AND SITE: I.P.

CONTROL INFORMATION: Vehicles only

DURATION OF EXPERIMENT: 4.5 hr

EXAM. TYPE: Neurochemistry

623<

Index

This index is an alphabetical listing of all of the chemicals for which extracts are presented, and some of their synonyms, and a tabular review of their chemical classes and induced effects. All of the studies in which human exposure was reported are also indicated.

The tabular review is not "all-inclusive." That is, not all chemical classes or types of effects are listed - only those that are of particular interest with respect to neurotoxicity. The codes for the chemical classes used are listed in Table 1. Brief definitions of the effects indexed are presented in Table 2.

Table 1. Chemical Class Codes

A	Acrylamides
Al	Aluminum and aluminum compounds
As	Arsenic and arsenic compounds
Au	Gold and gold compounds
B	Barbiturates
C	Carbamates
Ca	Calcium and calcium compounds
Cd	Cadmium and cadmium compounds
CN	Cyanides and nitriles
Co	Cobalt and cobalt compounds
Cu	Copper and copper compounds
Ga	Gallium and gallium compounds
Hg	Mercury and mercury compounds
HZ	Hydrazides
K	Ketones
Li	Lithium and lithium compounds
LSD	Lysergic acid derivatives
Mn	Manganese and manganese compounds
Ni	Nickel and nickel compounds
OP	Organophosphates
Pb	Lead and lead compounds
Sn	Tin and tin compounds
TA	Toxins, animal
TB	Toxins, bacterial
Te	Tellurium and tellurium compounds
TF	Toxins, fungus
Tl	Thallium and thallium compounds
TP	Toxins, plant
X	Halogenated hydrocarbons
Zn	Zinc and zinc compounds

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Table 2. Effects

CNS structural damage - gross or microscopic changes in the physical composition of the brain or spinal cord.

PNS structural damage - gross or microscopic changes in the physical composition of the peripheral nervous system.

Gross dysfunction - observed impaired or abnormal neuronal functioning that is discernable without special testing; for example, paralysis or convulsions.

Performance dysfunction - observed impaired or abnormal neuronal functioning that is discernable only by special performance tests, such as bar-walking or swimming tests.

Instrument detectable dysfunction - impaired or abnormal neuronal functioning that is detectable by direct instrumental measurement; for example, nerve conduction inhibition or EEG changes.

Cholinesterase inhibition - reduced activity and/or levels of cholinesterase.

Effects in offspring - abnormalities of the nervous system of offspring induced by exposure of the mother to the compound during gestation.

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Abate, see: Phosphorothioic acid, 0,0-dimethyl ester, 0,0-diester with 4,4'-thiodiphenol	948								
OP	Abathion, see: Phosphorothioic acid, 0,0-dimethyl ester, 0,0-diester with 4,4'-thiodiphenol	948								
	Acetaldehyde	1								
	Acetaldehyde, chloro-, (2,4-dinitrophenyl) hydrazone	2			2					
	Acetamide, 2-fluoro-N-methyl-N-1-napthyl	3			3					
	Acetanilide, 2'-(2'bromo-3-thienyl)thio-	4			4					
	Acetanilide, 4'-(4-(3-dimethyl amino) propyl)-1-piperazinyl)-	5	5							
	Acetanilide, 2'-(3-thienyl)thio-	6			6					
HZ	Acethydrazide	7			7					
	Acetic acid, bis(p-chlorophenyl)-	8								
HZ	Acetic acid, cyano-, hydrazide	9			9					
	Acetic acid, (2,3-dichloro-4-(2-methylene-butyrl)phenoxy)-	10			10					10
	Acetic acid, 2,4-dichlorophenoxy-	11-13			11 12 13					13
	Acetic acid, (2,4-dichlorophanoxy)-, compound with dimethylamine (1:1)	14			14					14

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Acetic acid, (ethylene-dinitrilo) tetra-	15	15						15	
	Acetic acid, fluoro-, sodium salt	16								
	Acetic acid, Iminodi	17					17			
Pb	Acetic acid, lead (2+) salt	18-24	22	23	21 22 24	19				
OP	Acetic acid, mercaptophenyl-, ethyl ester S-ester with 0,0-dimethyl phosphorodithioate	25			25			25		
Tl	Acetic acid, thallium (1) salt	26		26						
	Acetic acid, p-tolyl-, 3-alpha-tropanyl ester	27								
Zn	Acetic acid, zinc salt	28								
K	Acetone	29			29					29
HZ	Acetone, allophanylhydrazone	30			30					
HZ	Acetone semicarbazone	31			31					
HZ	Acetone, thiocarbohydrazone	32			32					
	Acetone, thiocarbohydrazonodi-	33			33					
HZ	Acetone thiosemicarbazone	34			34					
K	Acetophenone, 2-chloro	35								
HZ	Acetophenone, thiocarbohydrazone	36			36					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
A	Acrylamide	37-51	39 49	39 41 44 46 48 49 50 51	37 38 39 41 42 43 45 46 47 48 49 50 51	44				37 41 43
A	Acrylamide, N,N-diethyl-	52	52	52	52					
A	Acrylamide, N-hydroxymethyl-	53-54	54	54	54					
A	Acrylamide, N-methyl	55-56	56	56	55 56					
A	Acrylamide monomer	57			57					57
A	Acrylic acid, 2-cyano-, methyl ester	58-59		58	59					
	Actinomycin D	60								
	Adenosine, 3'-(alpha-amino-p-methoxy hydrocennamamido)-3'-deoxy-N,N-dimethyl	61-62						61 62		62
OP	Agritox, see: Phosphonothioic acid, ethyl-,O-ethyl O-(2,4,5-trichlorophenyl) ester	808-809								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
X	Agrocide, see: Cyclohexane, 1,2,3,4,5,6-hexachloro-,gamma-isomer	251-252								
	Alanine, 3-(3,4-dihydroxyphenyl)-, L	63								
	Alanine, 3-mercapto-, hydrogen sulfate (ester)	64	64							
	Alanine, N-methyl-3-sulfo-, L-	65			65					
	Alanine, phenyl-, L-	66-67	66							
	Alanine, 3-sulfino-	68-69	69							
	Alanine, 3-sulfo-, D-	70			70					
	Alanine, 3-sulfo-, L-	71-73	73		72					
	Alanine, 3-(2-thienyl)-	74							74	
	Alanine, 2,4,5-trihydroxyphenyl-	75-76	76	76		75				
	Alanine, 2,4,5-trihydroxyphenyl-, hydrobromide	77								
	Aldrin, see: 1,4:5,8-dimethanonapthalene, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-endo, endo-	293-294								
Hg	Alkyl mercury	78	78	78	78					
	Allocaine, see: Benzoic acid, p-amino-2-(diethylamino)ethyl ester	146								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
HZ	Allophanic acid, hydrazide	79			79					
TP	Aloes	80								80
Al	Aluminum hydroxide	81	81							
	N-Allylnormorphine HCl, see: Morphinan-3,6-alpha-diol, 17-allyl-7,8 didehydro-4,5-alpha-epoxy-, HCl	700								
	DL-alpha-Aminoadipic acid, see: Hexane-dioic acid, 2-amino-, DL-	454-456								
	6-Aminonicotinamide, see: 3-Pyridine-carboxamide, 6-amino-	1007-1010								
	DL-alpha-Aminopimelic acid, see: Heptane-dioic acid, 2-amino-, DL-	450-451								
	gamma-Aminopimelic acid, see: Heptane-dioic acid, 4-amino-	449								
	Amitriptyline, see: 5H-Dibenzo(a,d) cyclo-heptene-delta(sup 5),gamma-Propylamine, 10,11-dihydro-N,N-dimethyl-	267								
	Amitriptyline HCl, see: 5H-Dibenzo(a,d) cycloheptene-delta(sup 5),gamma-propyl-amine, 10,11-dihydro-N,N-dimethyl-, hydrochloride	268								
	Ammonium,(O-bromobenzyl)ethyldimethyl-, p-toluenesulfonate	82								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Ammonium, (3-carboxypropyl) trimethyl-, carboxylate	83								
	Ammonium, dibutyl(2-hydroxyethyl)methyl-	84						84		
	Ammonium, diethyl(2-hydroxyethyl)methyl-	85						85		
	Ammonium, (2-hydroxyethyl)triethyl-	86			86					
	Ammonium, (2-hydroxyethyl)triethyl-, p-toluenesulfonate,3,4,5-trimethoxy-benzoate	87			87					
Ca	Ammonium,(m-hydroxyphenyl)trimethyl-, bromide, dimethylcarbamate	88								
	Ammonium ion (+1)	89								
	Amphetamine, see: Phenethylamine, alpha-methyl-(+)-amphetamine	746								
	dl-Amphetamine SO4, see: Phenethylamine, alpha-methyl-,sulphate (2:1),(+,-)-	747-748								
	Amprolium, see: 2-Picolinium, 1-((4-Amino-2-propyl-5-pyrimidinyl)methyl)-, chloride, hydrochloride	971-972								
	Amyl nitrite, see: Nitrous acid, pentyl ester	713								
	Androst-5-en-3-beta-ol, 17-beta-((3-(dimethylamino)propyl)methylamino)-	90	90							

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Androst-5-en-17-one, 3-beta-hydroxy-, succinate, sodium salt	91			91					
	Angiotonin, see: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro-	1117-1121								
	Aniline, 4,4'-sulfonyldi-	92		92	92					92
	o-Anisamide, 4-amino-5-chloro-N-(2-diethylamino)ethyl)-	93			93					93
	Anthraquinone, dihydroxy-	94		94						94
	Aprobit, see: Phenothiazine, 10-(2-dimethylaminopropyl)-	782-783								
OP	Armin, see: Phosphonic acid, O-ethyl-O-(4-nitrophenyl)-ethyl ester	796								
As	Arsenic	95-96		95	95 96					95 96
	Artane, see: 1-Piperidinepropanol, alpha-cyclohexyl alpha-phenyl-, hydrochloride	982								
	L-Asparagine, see: Succinamic acid, alpha-amino-, L-	1098-1099								
	Aspartic acid	97	97							
	Aspartic acid, D-	98-100	100		98 99					
	Aspartic acid, DL-	101			101					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Aspartic acid, L-	102-104	104		102					
	Aspartic acid, N-acetyl-, L-	105-106								
	Aspartic acid, N-carbamoyl-, DL-	107								
	Aspartic acid, N,N-dimethyl-, D-	108			108					
	Aspartic acid, N,N-dimethyl-, DL-	109-110			109					
	Aspartic acid, N-ethyl, D-	111			111					
	Aspartic acid, N-ethyl-, DL-	112								
	Aspartic acid, N-ethyl, L-	113								
	Aspartic acid, N-formimino-, L-	114			114					
	Aspartic acid, N-iminomethyl-, D-	115								
	Aspartic acid, N-iminomethyl-, L-	116								
	Aspartic acid, N-methyl-, D-	117			117					
	Aspartic acid, N-methyl, DL-	118-119			118 119					
	Aspartic acid, alpha-methyl-, DL-	120								
	Aspartic acid, N-methyl-, DL-	121-122	121 122							
	Aspartic acid, N-methyl-, L-	123								
	Aspartic acid, N-propyl-, D-	124			124					
	Aspartic acid, N-propyl-, L-	125								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
TP	Atropine	126				126				126
TP	Atropinium, 8-methyl-, nitrate	127-128			128					
TP	Atropine SO4 (2:1)	129-130			130					
OP	Azinphosethyl, see: Phosphorodithioic acid, 0,0-diethyl ester, S-ester with 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3H)one	923-925								
OP	Azinphosmethyl, see: Phosphorodithioic acid, 0,0-dimethyl ester, S-ester with 3-(mercaptomethyl)-1,2,3-Benzotriazin-4(3H)-one	917								
OP	Azodrin, see: Phosphoric acid, dimethyl ester, ester with (E)-3-hydroxy-N-methyl crotonamide	850								
B	Barbital sodium, see: Barbituric acid, 5,5-diethyl-, sodium salt	133								
B	Barbituric acid, 5-allyl-5-(1-methylbutyl)-	131			131					
B	Barbituric acid, 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)-, sodium salt	132			132					
B	Barbituric acid, 5,5-diethyl-, sodium salt	133			133					
B	Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt	134-135			135				134	
B	Barbituric acid, 5-ethyl-5-(1-methyl-butyl)-2-thio-, sodium salt	136			136					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
B	Barbituric acid, 5-ethyl-5-phenyl-	137	137							
	Benadryl, see: Ethylamine, 2-(diphenyl-methoxy)-N,N-dimethyl-	357								
	Benzamide, p-amino-n-(2-(diethylamino)ethyl))-	138			138					138
	Benzenearsonic acid, 4-hydroxy-3-nitro-	139		139	139					
	Benzilic acid, 1-methyl-3-piperidyl ester, hydrochloride	140								140
	2-Benzimidazolinone, 1-(1-(3-(p-fluoro-benzoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl)-	141			141					141
>636	3H-1,4-Benzodiazepine, 7-chloro-2-methyl-amino)-5-phenyl-, 4-oxide	142-143			143	142				143
	2H-1,4-Benzodiazepin-2-one-7-chloro-1,3-dihydro-1-methyl-5-phenyl-	144			144					144
	Benzoic acid	145	145		145					
	Benzoic acid, p-amino-, 2-(diethylamino) ethyl ester	146			146					
HZ	Benzoic acid, hydrazide	147			147					
	Benzoxazole, 2-amino-5-chloro-	148			148					
	Benzydamine, see: 1H, Indazole, 1-Benzyl-3(3-(dimethylamino)propoxy)-	514								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Benzyl alcohol, 3,4-dichloro-alpha-((Isopropyl-amino)methyl)-, HCl	149								
	Benzyl alcohol, m-hydroxy-alpha-(methyl-amino)methyl-, hydrochloride, (-)-	150		150	150					150
	Benzylamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-	151								
	Benzylamine, N-methyl-N-2-propynyl-, HCl	152								
>287	Bicuculline	153-155			153 154					
	Biculline, see: Bicuculline	153-155								
	Biphenyl	156-157			156 157	156				156 157
X	Biphenyl, chloro	158			158					158
OP	Birlane, see: Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl)vinyl) diethyl ester	827								
	Bis(p-aminophenoxy) alkane series	159	159							
CN	Bis-beta-cyanoethylamine, see: Propio-nitrile, 3,3'-iminodi-	998-1003								
OP	Bis(3,5-dimethylphenyl)chlorophosphite, see: Phosphorochloridous acid, bis(3,5-xylyl) ester	902								
OP	Bithion, see: Phosphorothioic acid, O,O-dimethyl ester, O,O-diester with 4,4'-thiodiphenol	948								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
HZ	Biuret, diamino-	160			160					
	Boric acid	161-162	161 162		161 162					162
	Boric acid, tri-o-tolyl ester	163			163					
TB	Botulinum toxin type A	164-166		164	164 165 166					
	Bretylium tosylate, see: Ammonium (O-bromobenzyl) ethyldimethyl-, p-toluene sulfonate	82								
B	Brevital sodium, see: Barbituric acid, 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)-, sodium salt	132								
	Brisacodyl	167		167						167
LSD	Bromo-LSD, see: Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl-	299-305								
	alpha-Bungarotoxin	168			168					
OP	Butafex, see: Phosphorodiamidic fluoride, N,N'-dibutyl-	903								
	1,3-Butanediamine, N,N,N',N'-tetramethyl-	169			169					
	1,4-Butanediol	170				170				
	Butanol, see: Butyl alcohol	173								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	2-Butanol, 4-(dimethylamino)-3-methyl-1,2-diphenyl-,propionate(ester),HCl(+)-	171-172			171 172					172
OP	Butiphos, see: Phosphorotrithioic acid, S,S,S-tributyl ester	962								
	Butyl alcohol	173								
	n-Butylcholine, see: Ammonium, dibutyl (2-hydroxyethyl) methyl-	84								
	Butyric acid, 4-amino	174								
OP	Butyric acid, 2-amino-4-hydroxy-, phosphonate, (ester)	175								
	Butyric acid, 2-amino-4-sulfino-, DL-	176								
	Butyric acid, 2-hydrazino-2-methyl-	177			177					
	Butyric acid, 2-(methlyamino)-4-sulfo-, DL-	178								
Cd	Cadmium chloride	179-181	179 180 181							
TP	Caffeine	182			182					
Ca	Calcium chloride	183								
	Cannabidiol, see: Resorcinol, 2-p-mentha-1,8-dien-3-yl-5-pentyl-	1065-1066								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
C	Carbamic acid, diethylthio-, sodium salt	184-189	184 185 186 187 188 189	184 186	188					
C	Carbamic acid, ethyl ester	190								190
C	Carbamic acid, dimethyl-6-methyl-2-propyl-4-pyrimidnyl ester	191			191					
C	Carbamic acid, methyl-, benzo(b)thien-4-yl-ester	192-193			192 193					
C	Carbamic acid, methyl-, 5-sec-butyl-2-chlorophenyl ester	194			194					
C	Carbamic acid, methyl-m-sec-butylphenyl ester	195			195					
C	Carbamic acid, methyl-, m-cumenyl ester	196			196					
C	Carbamic acid, methyl-, 2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester	197			197					
C	Carbamic acid, methyl-, 4-dimethyl-amino-3,5-xylyl ester	198			198					
C	Carbamic acid, methyl-, m-(1-methyl-butyl)phenyl ester	199			199					
C	Carbamic acid, methyl-, 1-naphthyl ester	200-201	201		200 201			201		

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
C	Carbamic acid, methyl-, 3,4-5-trimethyl ester	202-203			202 203					
C	Carbaryl, see: Carbamic acid, methyl-, 1-naphthyl ester	200-201								
C	Carbofuran, see: Carbamic acid, methyl-2,3-dihydro-2,2-dimethyl-7-benzo-furanyl ester	197								
HZ	Carbohydrazide	204			204					
HZ	Carbohydrazide, thio-	205			205					
	Carbon dioxide	206			206					
	Carbon disulfide	207-213	207 208 212	209	207 208 209 210 211 213					210
	Carbonic acid, dithio-, cyclic S,S-(6-methyl-2,3-quinoxalinediyl) ester	214			214					
	Carbon monoxide	215-218	216 218	217 218	215 216 217 218					215 217 218
X	Carbon tetrachloride	219-222	219 222		222					219 222

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Carbophenothion, see: Phosphorodithioic acid, S-(p-chlorophenyl)thio methyl O,O-diethyl ester	908								
	Cardiotoxin	223					223			
	Cascara	224		224						224
C	Chevron RE 5305, see: Carbamic acid, methyl-, m-sec-butylphenyl ester	195								
C	Chevron RE 5655, see: Carbamic acid, methyl-, 5-sec-butyl-2-chlorophenyl ester	194								
	Chloramine, see: Diethylamine, 2,2'-dichloro-N-methyl-	286								
	Chlordiazepoxide, see: 3H-1,4-Benzodiazepine, 7-chloro-2-(methylamino)-5-phenyl-, 4-oxide	142-143								
	1-Chloro-amitriptyline, see: 5H-Dibenzo-(a,d)cycloheptene-delta(sup5, gamma) propyl-amine, 1-chloro-10,11-dihydro-N,N-dimethyl-	266								
	2-Chloroamphetamine, see: Phenethylamine, 2-chloro-2-methyl-, (+-)-	741								
	3-Chloroamphetamine, see: Phenethylamine, 3-chloro-2-methyl-,(+-)-	742								
	4-Chloroamphetamine, see: Phenethylamine, 4-chloro-2-methyl-,(+-)-	743								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	DL-p-Chloroamphetamine, see: Phenethyl-amine, 4-chloro-2-methyl-, DL-	739								
	p-Chloroamphetamine, see: Phenethylamine, 4-chloro-2-methyl-	743								
	beta-Chloroethylamine, ethyl-n-propyl-, HCl	225	225		225					
OP	Chlorofeninphos, see: Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl)vinyl diethyl ester	827								
	Chloroquine, see: Quinoline, 7-chloro-4((4-diethylamino)-1-methylbutyl)amino)-	1040								
OP	Chloroquine diphosphate, see: Quinoline, 7-chloro-4-(4-diethylamino-1-methyl-butylamino)-diphosphate	1039								
	Chlorphentermine, see: Phenethylamine p-chloro-alpha, alpha-'dimethyl-	738								
	Chlorpromazine, see: Phenothiazine, 2-chloro-10-3(3-dimethylamino)propyl)-	775-777								
	Chlorpromazine HCl, see: Phenothiazine, 2-chloro-10-(3-(dimethylamino)propyl)-, mono-hydrochloride	778-779								
	Chlorprothixene HCl, see: Thioxanthene-delta(sup9)-gamma-propylamine, 2-chloro-N,N-dimethyl, hydrochloride	1181								
	Choralose, alpha	226			226					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Cicutoxin, see: (-)-Heptadeca-trans-8, 10,12-triene-4,6-diyne-1,14-diol	448								
	Ciodrin, see: Crotonic acid, 3-hydroxy-, alpha-methylbenzyl ester dimethyl phosphate, (E)-	245								
	Citric acid, fluoro-	227-228	227		227 228					
	Clioquinol, see: 8-Quinolinol, 5-chloro-7-iodo-	1046-1051								
	Clomipramine, see: 5H-Dibenz(b,f)azepine, 3-chloro-5-(3-(dimethylamino)propyl)-10,11-dihydro-	263								
Co	Cobalt ion (+2)	229-230								
TA	Cobra toxin	231								
	Cocaine HCl, see: 1-alpha-H,5-alpha-H-Tropane-2-beta-carboxylic acid, 3-beta-hydroxy-methyl ester, benzoate (ester) hydrochloride	1193								
	Cocaine muriate, see: (same as above)	1193								
	Cogentin, see: 1-alpha-H,5-alpha-H Tropane 3-alpha-(diphenyl methoxy)	1194								
TP	Colchicine	232-233	232 233		233					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Cu	Copper (II) chloride	234					234			
Cu	Copper ion (+2)	235								
Cu	Copper II sulphate	236	236							
Cu	Copper (II) sulfate pentahydrate (1:1:5)	237	237							
	Cortisol	238								
	Cortisol, 21-acetate	239	239							
TP	Cottonseed oil	240			240					
OP	Coumaphos, see: Coumarin, 3-chloro-7-hydroxy-4-methyl, O-ester with O,O-diethyl phosphorothioate	242								
OP	Coumarin, 3-chloro-7-hydroxy-4-methyl-, bis(2-chloroethyl) phosphate	241		241	241					
OP	Coumarin, 3-chloro-7-hydroxy-4-methyl-, O-ester with O,O-diethyl phosphorothioate	242			242					
OP	Coumarin, 7-hydroxy-4-methyl-, bis(2-chloropropyl) phosphate	243	243	243	243					
	O-Cresol, 4,6-dinitro-	244			244					244
OP	Cresyl phosphate, see: Phosphoric acid, tolyl ester	862								
	Crotonic acid, 3-hydroxy-, alpha-methyl-benzylester, dimethyl phosphate, (F)-	245			245					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
TP	Crotyl theobromine, see: Theobromine, 1-(2-butenyl)-	1131								
OP	Crufomate, see: Phosphoramidic acid, methyl -4-tert-butyl-2-chlorophenyl methyl ester	816-817								
HZ	Cuprizone, see: Oxalic acid, bis(cyclo-hexylidenehydrazide)	721-724								
CN	Cyanic acid	246								
CN	Cyanide	247-249	247 248		249					
	Cycasin, see: beta-D-Glucopyranoside, (methyl-ONN-azoxy)methyl)-	381-384								
	1,3,5-Cycloheptatriene	250			250					
X	Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma-isomer	251-252			252		251			251
	Cycloheximide, see: Glutaramide, 3-(2-(3,5-dimethyl-2-oxocyclohexy)-2-hydroxyethyl)-	430-431								
	Cycloleucine, see: Cyclopentanecar-boxylic acid, 1-amino	254								
	5H-Cyclooct(b)indole, 5-(3-(dimethyl-amino)propyl)-6,7,8,9,10,11-hexahydro-	253	253							
	Cyclopentanecarboxylic acid, 1-amino	254	254							

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	Cyclopentane carboxylic acid, 1-phenyl-, 2-(diethylamino)ethyl ester, HCl	255				255				255
OP	Cyclophosphamide, see: 2H-1,3,2-Oxazaphosphorine, 2-(bis(2-chloroethyl)amino) tetrahydro-, 2-oxide	726								
	Cyclopropylamine, 2-phenyl-, sulfate trans- (+,-)-, (2:1)	256								
	D-Cysteic acid, see: Alanine, 3-sulfo-,D-	70								
	L-Cysteic acid, see: Alanine, 3-sulfo-,L-	71-73								
>479	Cysteine, L-	257-258	257 258							
	Cysteine, N-acetyl-, L-	259								
	L-Cysteine sulfinic acid, see: Alanine, 3-sulfino-	68-69								
	Cysteine-S-Sulphate, see: Alanine, 3-mercapto-, hydrogen sulfate (ester)	64								
	Dapsone, see: Aniline, 4,4'-sulfonyldi-	92								
	Darvon hydrochloride, see: 2-Butanol, 4-(dimethylamino)-3-methyl-1,2-diphenyl-, propionate (ester), hydrochloride, (+)-	171-172								
	DCPA, see: Acetic acid, 2,4-dichlorophenoxy-	11-13								
	DDA, see: Acetic acid, bis(p-chlorophenyl)-	8								

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X	DDT, see: Ethane, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-	314-322								
	Deanol, see: Ethanol, 2-dimethylamino-	327								
	Decaborane (14)	260			260					
	Decaborane, ethyl	261			261					
OP	DEF, see: Phosphorotrithioic acid, S,S,S-tributyl ester	962								
	Dehydroepiandrosterone, sodium succinate salt, see: Androst-5-en-17-one, 3-beta-hydroxy-, succinate, sodium salt	91								
	4-Deoxypyridoxine HCl, see: 3-Pyridine-methanol, 5-Hydroxy-4,6-dimethyl-, hydrochloride	1012								
	11-Desoxy-17-hydroxycorticosterone, sodium succinate salt, see: Pregn-4-ene-3,20-dione, 17,21-dihydroxy-, succinate, sodium salt	988								
	Dextropropoxyphene hydrochloride, see: 2-Butanol, 4-(dimethylamino-3-methyl-1, 2-diphenyl-, propionate (ester), hydrochloride (+)-	171-172								
	L-alpha-epsilon, 5th-Diaminopimelic acid see: Heptanedioic acid, 2,5-diamino-,L-	452								
	1,4-Diazabicyclo(2,2,2)octane	262					262			

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	20, 25-Diazacholesterol, see: Androst-5-en-3-beta-ol, 17-beta-((3-(dimethylamino) propyl)methylamino)-	90								
	Diazepam, see: 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-	144								
OP	Diazinon, see: Phosphorothioic acid, O,O-diethyl O-(2-isopropyl-6-methyl-4-pyrimidnyl) ester	939								
	Dibenamine, see: Dibenzylamine, N-(2-chloroethyl)-	285								
649	5H-Dibenz(b,f)azepine, 3-chloro-5-(3-(dimethylaminopropyl)-10,11-dihydro-	263	263							
	5H-Dibenz(b,f)azepine, 5-(3-(dimethyl-amino)propyl)-10,11-dihydro-	264				264				
	5H-Dibenz(b,f)azepine, 5-(3-(dimethyl-amino)propyl)-10,11-dihydro-mono-hydrochloride	265								
	5H-Dibenzo-(a,d)cycloheptene-delta (sup 5) gamma-propylamine 1-chloro-10,11-dihydro-N,N-dimethyl-	266	266							
	5H-Dibenzo(a,d)cycloheptene-delta (sup 5), gamma-propylamine, 10,11-dihydro-N,N-dimethyl-	267								
	5H-Dibenzo(a,d)cycloheptene-delta (sup 5), gamma-propylamine, 10,11-dihydro-N,N-dimethyl-, hydrochloride	268								

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650<	5H-Dibenzo(a,d)cyclohepten-5-one, 10,11-dihydro-,o-(2-(dimethylamino)ethyl)oxime	269								
	Dibenzo-p-dioxin,2,3,7,8-tetrachloro	270			270					270
	6H-Dibenzo(b,d)pyran-1-ol,3-(1'2'-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-	271				271				
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-7-alpha, 11-dihydroxy-6,6,9-trimethyl-3-pentyl	272			272					
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-7-beta, 11-dihydroxy-6,6,9-trimethyl-3-pentyl-	273			273					
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-8,11-dihydroxy-6,6,9-trimethyl-3-pentyl-	274			274					
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-11-hydroxy-6,6,9-trimethyl-3-pentyl-	275			275					
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-	276-277			276 277					
	6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6 aR-trans)-	278-284			279 282 284	278 280 283	281 282			278
	Dibenzylamine, N-(2-chloroethyl)-	285								
	n-Dibutylcholine, see: Ammonium, dibutyl (2-hydroxyethyl)methyl-	84								

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Sn	Dibutyltin oxide, see: Stannane, dibutyloxo-	1086								
	N,N-Dibutyltryptamine, see: Indole, 3-(2-(dibutylamino)ethyl)-	523								
OP	Dicapthon, see: Phosphorothioic acid, O-(2-chloro-4-nitrophenyl)O,O-dimethyl ester	936								
	Dichloroisoprenaline HCl, see: Benzyl alcohol, 3,4-dichloro-alpha-((Isopropyl-amino)methyl)-, hydrochloride	149								
	Dieldrin, see: 1,4:5,8-Dimethanonapthal-ene,1,2,3,4,10,10-hexachloro-6,7,epoxy-1,4,4a,5,6,7,8,8a-octahydro,endo,exo-	290-292								
OP	Diethion, see: Phosphorodithioic acid, S,S'-methylene 0,0,0',0'-tetraethyl ester	928-929								
	Diethylamine, 2,2'-dichloro-N-methyl-	286	286		286					
	beta-Diethylaminoethyl diphenylpropyl-acetate, see: Valeric acid, 2,2-di-phenyl-, 2-(diethylamino)ethyl ester	1223								
	Diethylcholine, see: Ammonium, diethyl (2-hydroxyethyl)methyl)-	85								
	Diethyl ether, see: Ethane, 1,1'-oxybis-	312-313								
	N,N-diethyltryptamine, see: Indole, 3-(2-(diethylamino)ethyl)-	524								

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652<	Diglycine, see: Acetic acid, iminodi	17								
	N,N-Dihexyltryptamine, see: Indole, 3-(2-dihexylaminoethyl)-	525								
	6,7-Dihydrodipyrido(1,2-a:2',1'-c) pyrazidiinium dibromide	287			287					
	7-alpha,11-Dihydroxy-delta(Sup8)tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol,6a,7,10,10a-tetrahydro-7-alpha,11-dihydroxy-6,6,9-trimethyl-3-pentyl-	272								
	7-beta-11-Dihydroxy-delta(Sup8)tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-7-beta,11-dihydroxy-6,6,9-trimethyl-3-pentyl-	273								
	8,11-Dihydroxy-delta(Sup9)tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-8,11-dihydroxy-6,6,9-trimethyl-3-pentyl-	274								
	5,6-Dihydroxytryptamine, see: Indole, 3-(2-aminoethyl)-5,6-dihydroxy-	516-518								
	5,7-Dihydroxytryptamine, see: Indole, 3-(2-aminoethyl)-5,7-dihydroxy-	519								
	Dilantin, see: Hydantoin, 5,5-diphenyl-, monosodium salt	488								
	Dimazine, see: Hydrazine, 1,1-dimethyl-	499-500								
	1,4:5,8-Dimethanonaphthalene, acetoxy-1, 2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-, exo-	288					288			

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	1,4:5,8-Dimethanonapthalene, 1,2,3,4,10, 10-hexachloro-6,7-epoxy-1,4,4a,5,6,7, 8,8a-octahydro-,endo,endo-	289					289			
	1,4:5,8-Dimethanonapthalene, 1,2,3,4,10, 10-hexachloro-6,7,epoxy-1,4,4a,5,6,7, 8,8a-octahydro,endo,exo-	290-292	292		291		290			
	1,4:5,8-Dimethanonapthalene, 1,2,3,4,10, 10-hexachloro-1,4,4a,5,8,8a-hexa-hydro-endo,endo-	293-294			293		294			293
	4-Dimethylamino-3,5 xylyl methylcarba-mate, 22.3% emulsifiable concentrate	295			295					
	Dimethylheptylpyran, see: 6H-Dibenzo(b,d) pyran-1-ol,3-(1',2'-dimethylheptyl)-7, 8,9,10-tetrahydro-6,6,9-trimethyl	271								
	Dimethyltryptamine, see: Indole, 3-(2-dimethylaminoethyl)-	526-528								
OP	Dimeton, see: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-methylacetamide	922								
OP	Dioxathion, see: Phosphorodithioic acid, O,O-diethyl ester, S,S-diester with p-dioxane-2,3-dithiol	916								
	Diquat, see: 6,7-Dihydrodipyrido(1,2-a: 2',1'-c)pyrazidiinium dibromide	287								
	Disipal, see: Fthylamine, N,N-dimethyl-2-(o-methyl-alpha-phenylbenzyl-oxy)-	355								

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	Distannoxane, hexabutyl-	296								
	Disulfide, bis(diethylthiocarbamoyl)	297			297					297
	Disulfiram, see: Disulfide, bis(diethylthiocarbamoyl)	297								
OP	Disulfoton, see: Phosphorodithioic acid, O,O-diethyl S-(2 ethylthio)ethyl)ester	918								
	L-Dopa, see: Alanine, 3-(3,4-dihydroxyphenyl)-, L-	63								
	Dormutil, see: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036								
	Droperidol, see: 2-Benzimidazolinone, 1-(1-(3-(p-fluorobenzoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl)-	141								
OP	Dursban, see: Phosphorothioic acid, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) ester	944-945								
OP	Dyvon, see: Phosphonic acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester	801								
	Edrophonium chloride, see: Ethyl(m-hydroxyphenyl)dimethylammonium chloride	362								
	EDTA, see: Acetic acid, (Ethylenedinitrilo)tetra-	15								
	Embutal, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt	134-135								

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	Endrin, see: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4, 4a,5,6,7,8,8a-octahydro-,endo,endo-	290-292								
	Ephedrine HCl	298								
OP	EPN, see: Phosphonothioic acid, phenyl-, O-ethyl O-(p-nitrophenyl) ester	812								
LSD	Ergoline-8-beta-carboxamide, 2-bromo-9,10-didehydro-N,N-diethyl-6-methyl-	299-305			305	302				
D	Ergoline-8-beta-carboxylic acid, 9,10-didehydro-6-methyl-, morpholide	306			306					306
	Ergotamine, dihydro-, monomethanesulfonate	307								
	D-Erythro-D-galacto-octo pyranoside, methyl 6,8-dideoxy-6-(1-methyl-4-propyl-2-pyrrolidine carboxamido)-1-thio-	308			308		308			
	Ethacrynic acid, see: Acetic acid, (2,3-dichloro-4-(2-methylenebutryl)phenoxy)-	10								
	Ethanamine	309					309			
X	Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-	310-311	310						311	
	Ethane, 1,1'-oxybis- (ether)	312-313	312		312 313					312

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
X	Ethane, 1,1,1-trichloro-2,2-bis (p-chloro-phenyl)-	314-322			314 317 319 320 321 322		316 318 320 321			
	Ethanol, see: Ethyl alcohol	333-350								
	Ethanol, 2-butylamino	323						323		
	Ethanol, 2-(p-chlorophenyl)-1-(p-(2-(diethylamino)ethoxy)phenyl)-1-p-tolyl-	324	324							
>656	Ethanol, 2-(dibutylamino)-	325						325		
	Ethanol, 2-(diethylamino)-	326						326		
	Ethanol, 2-dimethylamino-	327						327		
	Ethanol, 2-(ethylamino)-	328						328		
	Ethanol, 2-methoxy-	329-330			330	329 330				330
	Ethanol, 2-(methylamino)-	331						331		
	Ether, see: Ethane, 1,1'-oxybis-	312-313								
	Ether, chloromethyl methyl	332	332							
OP	Ethion, see: Phosphorodithioic acid, S,S'-methylene O,O,O'O'-tetraethyl ester	928-929								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>637<	Ethyl alcohol	333-350	334	344 350	333 343 344 346 349	337	346 350			337 344 346 350
	Ethylamine, see: Ethanamine	309								
	Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride	351	351		351					
	Ethylamine, 2-chloro-N,N-dipropyl-	352	352		352					
	Ethylamine, 2-chloro-N-ethyl-N-methyl-, hydrochloride	353	353		353					
	Ethylamine, N-chloro-methyl-N-propyl-2-, hydrochloride	354	354		354					
	Ethylamine, N,N-dimethyl-2-(o-methyl-alpha-phenylbenzyl-oxy)-	355				355				355
	Ethylamine, N,N-dimethyl-2-((o-methyl-alpha-phenylbenzyl)oxy)-, hydrochloride	356			356					356
	Ethylamine, 2-(diphenylmethoxy)-N,N-dimethyl-	357				357				357
	Ethylcholine, see: Ethyl(beta-hydroxy ethyl)trimethylammonium hydroxide	361								
	Ethylenediaminetetraacetic acid, see: Acetic acid, (ethylene-dionitrilo)tetra-	15								
	Ethylene glycol monomethyl ether, see: Ethanol, 2-methoxy-	329-330								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
X	Ethylene, tetrachloro-	358			358					358
X	Ethylene, trichloro-	359-360	359		359 360					359 360
	Ethyl (beta-hydroxy ethyl)trimethyl-ammonium hydroxide	361						361		
	Ethyl (m-hydroxyphenyl) dimethyl-ammonium chloride	362								
	alpha-Ethyltryptamine acetate, see: Indole, 3-(2-aminobutyl)-, monoacetate	515								
	Ethylurethan, see: Carbamic acid, ethyl ester	190								
	Etryptamine, see: Indole, 3-(2-amino-butyl)-, monoacetate	515								
OP	Fenthion, see: Phosphorothioic acid, 0,0-dimethyl-,0-(4-methylthio)-m-tolyl) ester	954-955								
	5-Fluoroorotic acid, see: 4-Pyrimidine carboxylic acid, 1,2,3,6-tetrahydro-2, 6-dioxo-5-fluoro-	1023-1024								
X	Fluorothane, see: Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-	310-311								
	Folic acid	363			363					
	Folic acid, sodium salt	364								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Formaldehyde	365								
	Formamidine, see: Imidazole	509								
	Formanilide, 2'-(3-bromo-2-thienyl)thio-	366			366					
	Formanilide, 2'-(3-bromo-4-thienyl)thio-	367			367					
	Formanilide, 2'-(2-bromo-3-thienyl)thio-5'-chloro-	368			368					
	Formanilide, 2'-(3-bromo-2-thienyl)thio-5'-chloro-	369			369					
>659	Formanilide, 2'-(3-bromo-4-thienyl)thio-5'-chloro-	370			370					
	Formanilide, 2'-(2-bromo-3-thienyl)thio-5'-(trifluoromethyl)-	371			371					
	Formanilide, 5'-chloro-2'-(3-thienyl)thio-	372			372					
	Formanilide, 2'-(3-thienyl)thio-5'-(trifluoromethyl)-	373			373					
	Furacin, see: Benzyl alcohol, m-Hydroxy-alpha-(methylamino)methyl)-, hydrochloride, (-)-	150								
C	Furadan, see: Carbamic acid, methyl-, 2, 3-dihydro-2,2-dimethyl-7-benzofuranyl ester	197								
HZ	Furoyl hydrazide	374			374					
	GABA, see: Butyric acid, 4-amino	174								

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	Galactose	375								
	D-Galactose	376-377								
	Galactosiduronic acid, methyl-, methyl ester, polymer of sulfated sodium salt	378			378					
Ga	Gallium fluoride	379			379					379
	Gasoline	380					380			
>099	beta-D-Glucopyranoside, (methyl-ONN-azoxy)methyl)-	381-384	381 382 384		381 382 383 384					
	Glue vapors	385		385	385					385
OP	Glutaconic acid, 3-hydroxy-, dimethyl ester, dimethyl phosphate	386			386					
	Glutamic acid	387-388	387							
	Glutamic acid, D-	389-391	391				389 390			
	Glutamic acid, DL-	392					392			
	Glutamic acid, L-	393-395	395				393 394			
	Glutamic acid, N-acetyl	396					396			
	Glutamic acid, N-acetyl, L-	397								
	Glutamic acid, 3-amino-	398					398			

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	Glutamic acid, N-carbamoyl-, L-	399					399			
	Glutamic acid, N-(p-(((2,4-diamino-6-pteridnyl)methyl)methylamino)benzoyl)-L-	400-401	400 401		400					401
	Glutamic acid, N,N-dimethyl-, L-	402					402			
	Glutamic acid, hydrazide, L-	403					403			
	Glutamic acid, beta-hydroxy	404					404			
	Glutamic acid, N-methyl-, D-	405					405			
	Glutamic acid, alpha-methyl-, DL-	406-407					406			
	Glutamic acid, N-methyl-, DL-	408-410	410				408 409			
	Glutamic acid, alpha-methyl ester, L-	411					411			
	Glutamic acid, gamma-methyl ester, L-	412					412			
	Glutamic acid, monosodium salt, L-(+)-	413-424	414 415 416 417 418 419 420 421 424		413 414 420		413			
	Glutamic acid, sodium salt	425					425			
	Glutamine, L-	426-427					426			

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	Glutamine, N,N-dimethyl-, L-	428					428			
	Glutamine, N-methyl-, L-	429					429			
	alpha-Glutarobetaine, see: Ammonium, (3-Carboxypropyl)trimethyl-, carboxylate	83								
	Glutaramide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxymethyl)-	430-431			430	430		431		431
	Glutaric acid	432					432			
	Glutaric acid, 2-oxo-	433								
	Glutarimide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl)	434				434				
662<	Glutarimide, 3-ethyl-3-methyl-	435			435		435			435
	Gluterimide, 2-ethyl-2-phenyl-	436-438			436 437 438		437			436 437
	Glutethimide, see: Gluterimide, 2-ethyl-2-phenyl-	436-438								
	Glycine, N-allyl-	439-440	440		439 440		439 440			
	Glycine, N-(gamma-glutamyl)-, L-	441					441			
HZ	Glycolic acid, hydrazide	442			442					
	Glyoxalin, see: Imidazole	509								

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Au	Gold	443		443	443		443			443
	Guanethidine SO4, see: Guanidine, (2-(hexahydro-1(2H)azocinyl)ethyl)-, sulphate (2:1)	444								
	Guanidine, (2-hexahydro-1(2H)azocinyl) ethyl)-, sulphate (2:1)	444								
OP	Guthion, see: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 3-(mercapto-methyl)-1,2,3 benzotriazin-4 (3H)-one	923-925								
OP	Gutoxon, see: Phosphorothioic acid, O,O-dimethyl S-((4-oxo-1,2,3-benzotriazin-3(4H)-yl)methyl) ester	959								
X	Halothane, see: Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-	310-311								
OP	Haloxon, see: Coumarin, 3-chloro-7-hydroxy-4-methyl-, bis(2-chloroethyl) phosphate	241								
X	Halsan, see: Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-	310-311								
	Harmidine, see: 3H-Pyrido-(3,4-b) indole, 4,9-dihydro-7-methoxy-1-methyl-	1015								
	Harmine, see: 9H-Pyrido(3,4-b) indole, 7-methoxy-1-methyl-	1016								
	Harmine HCl, see: 9H-Pyrido(3,4-b) indole, 7-methoxy-1-methyl-, hydrochloride	1017								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Harmol, see: 9H-Pyrido(3,4-b)indol-7-ol, 1-methyl-	1020								
	Harrisite	445			445		445			445
	HCP, see: Phenol, 2,2'-methylene bis (3,4,6-trichloro)-	756-772								
	HEF-2 (mix of alkylpentaborane derivatives)	446			446					
	Hemicholinium-3, see: Morpholinium, 2,2'-(4,4'-biphenylylene)bis(2-hydroxy-4,4-dimethyl-, dibromide	707								
TB	alpha-Hemolysin from staphylococcus aureus	447					447			
	Heptachlor, see: 4,7-Methanoindene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-	690-691								
	(-)-Heptadeca-trans-8,10,12-triene-4,6-diyne-1,14-diol	448			448		448			448
	Heptanedioic acid, 4-amino-	449					449			
	Heptanedioic acid, 2-amino-, DL-	450-451					450			
	Heptanedioic acid, 2,5-diamino-, L-	452					452			
X	gamma-Hexachlorocyclohexane, see: Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma isomer	251-252								
	Hexachlorophane, see: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-	756-772								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Hexadrin, see: 1,4:5,8-Dimethanonapthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4, 4a,5,6,7,8,8a-octahydro-,endo,endo-	290-292								
	Hexamidone, see: 4,6(1H,5H)-Pyrimidinedione, 5-ethyldihydro-5-phenyl-	1025								
	Hexane	453		453	453					453
	Hexanedioic acid, 2-amino-, DL-	454-456					454			
K	2,5-Hexanedione	457-458		458	457 458					
K	2-Hexanone	459-465		461 463 464 465	459 460 462 463 464 465		459 460 463 464			459 460 463
	Hexone, see: 2-Pentanone, 4-methyl-	736								
	HiCal-2	466			466					
	Holothurin A	467					467			
	D-Homocysteic acid	468					468			
	DL-Homocysteic acid	469-470	470				469			
	L-Homocysteic acid	471					471			

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>999	Hydantoin, 5,5-diphenyl-	472-487	473 474 475 486		472 473 474 475 476 477 478 479 483 484 485		472 479 480 481 482 483 484 485 486			472 475 476 477 478 479 481 482 483 484 485
	Hydantoin, 5,5-diphenyl-monosodium salt	488	488		488					488
	Hydantoin, 1-((5-nitrofurfurylidene) amino)-	489-498		490 494 496 497	491 492 494 495 496 497		490 492 493 498			489 491 492 493 494 495 496 497 498
	Hydrazine, 1,1-dimethyl-	499-500			499 500					
	Hydrazine, hydrochloride	501			501					
	Hydrazine, (alpha-methylphenethyl)-, hydrochloride	502								
	Hydrazine, phenethyl-, hydrochloride	503								
	Hydrazoic acid	504			504					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
CN	Hydrocyanic acid	505-506	505 506							
	Hydrogen selenide	507			507					507
	Hydrogen sulfide	508			508					508
	5-Hydroxydimethyltryptamine, see: Indol-5-ol, 3-02-(dimethylamino)ethylo-	531								
	6-Hydroxydopa, see: Alanine, 2,4,5-trihydroxyphenyl-	75-76								
>299	6-Hydroxydopamine, see: Pyrocatechol, 4-(2-aminoethyl)-5-hydroxy-	1026-1028								
	6-Hydroxydopamine hydrobromide, see: Alanine, 2,4,5-trihydroxyphenyl-, hydrobromide	77								
	11-Hydroxy-delta(Sup8)tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-11-hydroxy-6,6,9-trimethyl-3-pentyl-	275								
	Hyminal, see 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036								
OP	Imidan, see: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with N-(mercaptomethyl) phthalimide	926								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Imidazole	509			509		509			
	Imidazole, 1-methyl-	510			510		510			
	Imidazole, 2-methyl-	511			511		511			
	Imidazole, 4-methyl-	512			512		512			
	2-Imidazoline-2-benzyl-hydrochloride	513								
>899	Imipramine, see: 5H-Dibenz(b,f)azepine, 5-(3-(dimethylamino)propyl)-10,11-dihydro-	264								
>899	Imipramine HCl, see: 5H-Dibenz(b,f) azepine, 5-(3-(dimethylamino)propyl)-10,11-dihydro-, monohydrochloride	265								
	1H-Indazole, 1-benzyl-3(3-(dimethylamino) propoxy)-	514			514					
OP	Indocybin, see: Indol-4-ol,3-(2-(dimethyl amino)ethyl)-, dihydrogen phosphate	533-534								
	Indole, 3-(2-aminobutyl)-, monoacetate	515					515			
	Indole, 3-(2-aminoethyl)-5,6-dihydroxy-	516-518								
	Indole, 3-(2-aminoethyl)-5,7-dihydroxy-	519	519		519					
	Indole, 3-(2-aminoethyl)-5-methoxy-	520				520				520
	Indole, 3-(2-aminoethyl)-6-methoxy-	521				521				521
	Indole, 3-(2-aminopropyl)-, acetate	522					522			

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>699	Indole, 3-(2-(dibutylamino)ethyl)-	523			523					523
	Indole, 3-(2-(diethylamino) ethyl)-	524			524					524
	Indole, 3-(2-dihexylaminoethyl)-	525			525					525
	Indole, 3-(2-dimethylaminoethyl)-	526-528			526 528	527	526			527 528
	Indole, 3-(2-(dimethylamino)ethyl)-5-methoxy-	529			529		529			
	Indole, 3-(2-dipropyl amino)ethyl)-	530			530					530
	Indol-5-ol, 3-(2-(dimethylamino)ethyl)-	531			531		531			
	Indol-4-ol, 3(2-(dimethyl amino)ethyl)-	532			532					
OP	Indol-4-ol, 3-(2-(dimethylamino)ethyl)-, dihydrogen phosphate	533-534			533 534		534			
	Iprindole, see5H-Cyclooct(b) indole, 5-(3-(dimethylamino)propyl)-6,7,8,9, 10,11-hexahydro-	253								
HZ	Iproniazid PO4, see: Isonicotinic acid, 2-isopropyl hydrazide phosphate	558								
	Isocyanic acid, p-bromophenyl ester	535	535		535					
	Isocycloheximide, see: Glutarimide, 3-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl)-	434								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Isoglutamine, L-	536					536			
OP	Isomethylsystox, see: Phosphorothioic acid, 0,0-dimethyl S-(2-ethylthioethyl) ester	951								
OP	Isomethylsystox sulfone, see: Phosphorothioic acid, 0,0-dimethyl S-(2-(ethyl sulfonyl)ethyl)ester	950								
HZ	Isoniazid, see: Isonicotinic acid, hydrazide	538-557								
HZ	Isonicotinic acid, 2-(2-(benzylcarbamoyl) ethyl) hydrazide	537								
HZ	Isonicotinic acid, hydrazide	538-557	539 540 541 547 549	538 542 544 548 551 552 553 554 555	539 540 541 542 543 545 546 550 556 557	538	544 550			543 546 548 550 556 557
HZ	Isonicotinic acid 2-isopropyl hydrazide phosphate	558								
HZ	Isonicotinic acid, 2-(sulfomethyl) hydrazide, sodium salt	559-560	560							
	JB-336, see: Benzilic acid, 1-methyl-3-piperidyl ester, hydrochloride	140								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	JB-468, see: 3-Piperidinol, 1-methyl-, citrate	984								
	Kainic acid, see: 3-Pyrrolidineacetic acid, 2-carboxy-4-isopropenyl	1031								
	Kemadrin, see: 1-Pyrrolidine propanol, alpha-cyclohexyl-alpha-phenyl-	1034								
	Alpha-Ketoglutaric acid, see: Glutaric acid, 2-oxo-	433								
	Kryptopyrrole, see: Pyrrole, 2,4-dimethyl -3-ethyl-	1030								
HZ	Lactic acid, hydrazide	561			561					
Pb	Lead	562-578	567 571 577	564	562 564 569 571 572 575	565 573	573 576			562 563 564 566 568 571 572 573 575 576 578
Pb	Lead acetate, trihydrate	579	579							
Pb	Lead,bis (acetato) tetrahydrooxytri	580	580		580					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Pb	Lead carbonate	581-587	581 582 583 584 585 586		581 582 583	586 587			586 587	
Pb	Lead (II) nitrate (1:2)	588	588							
Pb	Lead subacetate, see: Lead, bis(acetato) tetrahydrooxytri	580								
TP	Leurocristine	589-598	593 598	589 590 591 595 596 597 598	589 592 595 596 598	591 595	591 594 595		593 594	591 592 594 595 596 597
TP	Leurocristine, sulfate (1:1) (salt)	599-604	604	600 601 602 603	599 600 602					602
	Librium, see: 3H-1,4-Benzodiazepine, 7-chloro-2-(methylamino)-5-phenyl-, 4-oxide	142-143								
	Lincomycin, see: D-Erythro-D-Galacto-octo pyranoside, methyl 6,8-dideoxy-6-(1-methyl)-4-propyl-2-pyrrolidine-carboxamido)-1-thio	308								
X	Lindane, see: Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma isomer	251-252								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Lindol, see: Phosphoric acid, tritolyl ester	873-875								
Li	Lithane, see: Lithium carbonate	605								
Li	Lithium carbonate	605			605					605
Li	Lithium chloride	606				606				
B	Luminal, see: Barbituric acid, 5-ethyl-5-phenyl-	137								
LSD	D-Lyseramide, N-N-diethyl ester, tartrate	607								
LSD	Lysergic acid diethylamide tartarate, see: D-Lyseramide, N-N-diethyl ester, tartrate	607								
D	d-Lysergic acid, morpholide, see: Ergoline -8-beta-carboxylic acid,9,10-didehydro-6-methyl-, morpholide	306								
	Malathion, see: Succinic acid, mercapto-, diethyl ester, S-ester with O,O-dimethyl phosphorodithioate	1103-1106								
	Malic acid, L(+)-	608					608			
	Malonic acid	609					609			
	Malonic acid, amino-	610					610			
	Malonic acid, aminoethyl-	611					611			
HZ	Mandelic acid, hydrazide	612			612					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Mn	Manganese	613-620			613 614 618 619 620		615			613 614 618 619 620
Mn	Manganese (II) chloride (1:2)	621-622	621		621		621 622			
Mn	Manganese, cyclopentadienyltricarbonyl	623			623					
OP	Menazon, see: Phosphorodithioic acid, S-((4,6-diamino-S-triazin-2-yl)methyl) O,O-dimethyl ester	912								
	3-Mercaptopropionic acid	624			624					
Mn	Manganese dioxide	625			625					625
	Menesulfate, see: Galactosiduronic acid, methyl-, methyl ester, polymer of sulfated sodium salt	378								
	Mephenolaxone, see: 2-Oxazolidinone, 5-((O-methoxyphenoxy)methyl)	727								
C	Meprobamate, see: 1,3-Propanediol, 2-methyl-2-propyl-, dicarbamate	991								
	Mepyramine maleate, see: Pyridine, 2-(dimethylamino)ethyl)(p-methoxybenzyl) amino)-, maleate (1:1)	1011								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	MER-16, see: 2-Piperidineethanol, alpha, alpha, diphenyl-1-methyl-, hydrochloride	981								
OP	Mercaptophos, see: Phosphorothioic acid, O,O-dimethyl-, O-(4-methylthio)-m-tolyl) ester	954-955								
	3-Mercaptopropionic acid	626-627			626		626			
	Mercapturic acid, see: Cysteine, N-acetyl-, L-	259								
Hg	Mercuric bichloride	628-630	628 629							
Hg	Mercuric (II) nitrate	631								
Hg	Mercury	632-636	632		633 635 636		636			632 633 635 636
Hg	Mercury, (acetato)methyl-	637-638	637 638		637					
Hg	Mercury, butyl-chloro-	639								
Hg	Mercury (I) chloride	640	640		640					640
Hg	Mercury (II) chloride	641	641	641						
Hg	Mercury, chloroethyl-	642-644	642 643		642					642

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Hg	Mercury, chloromethyl-	645-656	645 646 648 650 651 652 653 654 655	649	649 650 652	655			651 654	
Hg	Mercury, chlorophenyl	657								
Hg	Mercury, (3-cyanoguanidino)methyl-	658-661	658 659 660	658 659	658 660 661				661	
Hg	Mercury, cysteinylethyl-	662	662							
Hg	Mercury, ((2,3-dihydroxypropyl)thio) methyl-	663	663	663		663				
Hg	Mercury, hydroxymethyl-	664-667	664 665 666	666	666	664 665				
Hg	Mercury, mercaptomethyl-	668-669		668 669						
Hg	Mercury, methyl-	670-680	675 676		671 675 677 678	679 680	678 680		676	676 677 678
Hg	Mercury, methyl(methylthio)-	681	681	681						

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Hg	Mercury, methyl(thioacetamido)-	682-684	682 683		682 683					682
OP	Merphos, see: Phosphorotrithious acid, tributyl ester	963								
	Mescaline, see: Phenethylamine, 3,4,5-trimethoxy-	749-751								
	Mescaline hemisulfate, see: Phenethylamine, 3,4,5-trimethoxy-, hemisulfate	752								
OP	Metasystox-R, see: Phosphorothioic acid, O,O-dimethyl S-(2-(ethylsulfinyl)ethyl) ester	949								
	Metamphetamine hydrochloride, see: Phenethylamine, N-alpha-dimethyl-, hydrochloride, (-)-	744-755								
X	Methane, bromo-	685-686			685 686					685 686
X	Methane, chloro-	687			687					687
X	Methane, dichloro-	688-689				688 689				688 689
	4,7-Methanoindene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-	690-691	690		691					
	4,7-Methanoisobenzofuran, 1,3,4,5,6,7,8,8-octachloro-1,3,3a,4,7,7a-hexahydro	692			692					

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Methanol	693-697	693 694		694 695 696					693 694 695 696
	Methaqualone, see: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036								
	beta-Methasone, see: 16-methylprepna-1,4-diene-3,20-dione, 9-fluoro-11,17, 21-trihydroxy-	698								
OP	Methion, see: Phosphorothioic acid, O,O-dimethyl O-(4-nitro-m-tolyl)ester	958								
	Methionine sulfoximine, see: Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-	1107-1111								
>879	Methotrexate, see: Glutamic acid, N-(p-(((2,4-diamino-6-pteridnyl)methyl) methylamino)benzoyl)- L-	400-401								
	5-Methoxydimethyltryptamine, see: Indole, 3-(2-dimethylamino)ethyl)-5-methoxy-	529								
	5-Methoxytryptamine, see: Indole, 3-(2-aminoethyl)-5-methoxy-	520								
	6-Methoxytryptamine, see: Indole, 3-(2-aminoethyl)-6-methoxy-	521								
	3-Methoxytyramine, see: Phenol, p-(2-aminoethyl)-3-methoxy-	754								
X	Methyl bromide, see: Methane, bromo-	685-686								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
K	Methyl-N-butyl ketone, see: 2-Hexanone	459-465								
	Methyl cellosolve, see: Ethanol, 2-methoxy-	329-330								
X	Methyl chloride, see: methane, chloro-	687								
	N-Methyl-L-cysteic acid, see: Alanine, N-methyl-3-sulfo-, L-	65								
X	Methylene chloride, see: Methane, dichloro-	688-689								
	Methyl glycol, see: Ethanol, 2-methoxy-	329-330								
	N-Methyl-DL-homocysteic acid, see: Butyric acid, 2-(methylamino)-4-sulfo-, DL-	178								
	Methyl iso-butyl ketone, see: 2-Pentanone, 4-methyl-	736								
Hg	Methyl mercuric acetate, see: Mercury, (acetato)methyl-	637-638								
Hg	Methylmercuric sulfide, see: Mercury, mercaptomethyl-	668-669								
Hg	Methylmercury dicyandiamide, see: Mercury, (3-cyanoguanidino) methyl-	658-661								
Hg	Methyl methylmercury sulfide, see: Mercury, methyl (methylthio)-	681								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Methyl parathion, see: Phosphorothioic acid, 0,0-dimethyl 0-(p-nitrophenyl) ester	957								
	Methyl phenidate HCl, see: 2-Piperidine acetic acid, alpha-phenyl-,methyl ester, hydrochloride	979								
	16-Methylpregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy	698	698			698				
TP	Methyl theobromine, see: Caffeine	182								
OP	Methyl trithion, see: Phosphorodithioic acid, S-(((p-chlorophenyl)thio)methyl) 0,0-dimethyl ester	910-911								
	alpha-Methyltryptamine acetate, see: Indole, 3-(2-aminopropyl)-, acetate	522								
	2-Methyoxyacridine, 6-chloro-9-((4-(diethylamino)-1-methylbutyl)amino)-, dimethane sulfonate	699								
	Metoclopramide, see: o-Anisamide, 4-amino-5-chloro-N-(2-diethylamino)ethyl)	93								
	Metrazol, see: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro	1117-1122								
	Miazole, see: Imidazole	509								
C	Moham, see: Carbamic acid, methyl-, benzo(b)thien-4-yl-ester	192-193								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
681	Morestan, see: Carbonic acid, dithio-, cyclic S,S-(6-methyl-2,3-quinoxaline-diyl) ester	214								
	Morphinan-3,6-alpha-diol,17-allyl-7, 8 didehydro-4,5-alpha-epoxy-, HCl	700					700			
	Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha-epoxy-17-methyl-	701								
	Morphinan-3,6-diol,7,8-didehydro-4,5-epoxy-17-methyl-, hydrochloride, (5-alpha-6-alpha)-	702								
	Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha epoxy-17-methyl-, sulfate	703-704					704			
	Morphinan-6-one, 4-5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydro-chloride, (5-alpha)-	705			705					
	Morphine HCl, see: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, hydrochloride, (5-alpha-6-alpha)-	702								
	Morphine sulfate, see: Morphinan-3,6-alpha-diol, 7,8-didehydro-4,5-alpha epoxy-17-methyl-, sulfate	703-704								
	Morpholine, 2-chloroethyl-, hydrochloride	706	706		706					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Morpholinium, 2,2'-(4,4'-biphenylylene) bis(2-hydroxy-4,4-dimethyl-, dibromide)	707					707			
	MSG, see: Glutamic acid, monosodium salt, L-(+)-	413-424								
	MTX, see: Glutamic acid, N-(p-(((2,4-diamino-6-pteridnyl)methyl)methylamino) benzoyl)-, L-	400-401								
	Mustargen, see: Diethylamine, 2,2'-dichloro-N-methyl-	286								
	Mytilus edulis toxins	708			708		708			708
OP	Naled, see: Phosphoric acid, 1,2-dibromo-2,2-dichloroethyl dimethyl ester	840								
	Naloxone HCl, see: Morphinan-6-one, 4-5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5-alpha)-	705								
	Napthalene methanol, alpha-(isopropyl-amino) methyl-, hydrochloride	709								
OP	Napthalimide, N-hydroxy-, diethyl phosphate	710			710					
OP	Nemacide, see: Phosphorothioic acid, O-(2,4-dichloro-phenyl)-O,O-diethyl ester	938								
B	Nembutal, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt	134-135								
	Neomycin	711			711		711			

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Ca	Neostigmine bromide, see: Ammonium, (m-hydroxyphenyl)trimethyl-, bromide dimethylcarbamate	88								
HZ	Neotizide, see: Isonicotinic acid, 2-(sulfomethyl)hydrazide, sodium salt	559-560								
HZ	Nialamide, see: Isonicotinic acid, 2-(2-(benzylcarbamoyl)ethyl)hydrazide	537								
OP	Nialate, see: Phosphorodithioic acid, S,S'-methylene 0,0,0',0'-tetraethyl ester	928-929								
Ni	Nickel	712								
	Nigrin, see: Picolinic acid, 5-amino-6-(7-amino-5,8-dihydro-6-methoxy-5,8-dioxo-2-quinolyl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methyl	969								
	Nissol, see: Acetamide, 2-fluoro-N-methyl-N-1-napthyl-	3								
	Nitrofurantoin, see: Hydantoin, 1-((5-nitrofurfurylidene)amino)-	489-498								
OP	Nitrophos, see: Phosphorothioic acid, 0,0-dimethyl 0-(4-nitro-m-tolyl) ester	958								
	Nitrous acid, pentyl ester	713			713					
	Nivemycin, see Neomycin									
	2,Norbornene, 1,2,3,4,7,7-hexachloro-5,6-bis(chloromethyl)-	714			714					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
TA	Notechis scutatus scutatus venom	715-716			716		715 716			
	Novocaine, see: Benzamide, p-amino-n-(2-(diethylamino)ethyl))-	138								
	Noxiptiline, see: 5H-Dibenzo(a,d)cyclo-hepten-5-one, 10,11-dihydro-,O-(2-(dimethylamino)ethyl)oxime	269								
OP	Organophosphate pesticides	717								717
	Orphenadrine HCl, see: Ethylamine, N,N-dimethyl-2-((o-methyl-alpha-phenylbenzyl) oxy)-, hydrochloride	356								
	Orthonal, see: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036								
	Ouabain	718-720	720		719					
HZ	Oxalic acid, bis(cyclohexylidenehydrazide)	721-724	721 723 724	721	723 724					
HZ	Oxalic acid, dihydrazide	725			725					
OP	2H-1,3,2-Oxazaphosphorine, 2-(bis(2-chloroethyl)amino)tetrahydro-, 2-oxide	726	726							
	2-Oxazolidinone, 5-((O-methoxyphenoxy) methyl)	727			727					
	2-Oxazoline, 2-amino-5-phenyl-	728			723					728

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Oxygen	729-732			729 731 732					729
	Ozone	733					733			
	Pagitane, see: 1-Piperidine propanol, alpha-cyclopentyl-alpha-phenyl-	983								
	2-PAMM, see: Pyridinium, 2-formyl-1-methyl -,methanesulfonate, oxime	1014								
	Panparnit, see: cyclopentane carboxylic acid, 1-phenyl-, 2-(diethylamino)ethyl ester, hydrochloride	255								
OP	Papthion, see: Acetic acid, mercapto-phenyl-, ethyl ester, S-ester with 0,0-dimethyl phosphorodithioate	25								
OP	Paraoxon, see: Phosphoric acid, diethyl p-nitrophenyl ester	846								
OP	Parathion, see: Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester	941-943								
	Pargyline HCl, see: Benzylamine, N-methyl-N-2-propynyl-, hydrochloride	152								
	Parsidol, see: Phenothiazine, 10-(2-diethylamino)propyl)-	782-783								
	Penicillin G, see: 4-Thia-1-azabicyclo (3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-	1136-1138								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Pentaborane (9)	734-735			734 735		735			735
	Pentamethylenetetrazole, see: 5H-Tetrazoloazepine, 6,7,8,9-tetrahydro	1117-1122								
	2-Pentanone, 4-methyl-	736		736						
	Pentaphane hydrochloride, see: Cyclopentane carboxylic acid, 1-phenyl-, 2-(diethylamino)ethyl ester, HCl	255								
B	Pentobarbital sodium, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt	134-135								
	Perphenazine, see: 1-Piperazineethanol, 4-(3-(2-chlorophenothiazin-10-yl)propyl)	977								
>989	Perphenazine enanthate, see: 1-Piperazineethanol, 4-(3-(2-chlorophenothiazin-10-yl)propyl)-, heptanoate	978								
	Pesticides (unspecified)	737					737			737
	Phenelzine HCl, see: Hydrazine, phenethyl-, hydrochloride	503								
	Phenethylamine, p-chloro-alpha, alpha-dimethyl	738	738							
	Phenethylamine, 4-chloro-2-methyl-, DL-	739	739							
	Phenethylamine, 4-chloro-alpha-methyl-	740								
	Phenethylamine, 2-chloro-2-methyl-, (+-)-	741								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Phenethylamine, 3-chloro-2-methyl-,(+-)-	742								
	Phenethylamine, 4-chloro-2-methyl-,(+-)-	743								
	Phenethylamine, N-alpha-dimethyl-, hydrochloride, (-)-	744-745			744 745				744	
	Phenethylamine, alpha-methyl-(+)- amphetamine	746								
	Phenethylamine, alpha-methyl-sulphate (2:1), (+,-)-	747-748				748	748			
>687	Phenethylamine, 3,4,5,-trimethoxy-	749-751			749				751	
	Phenethylamine, 3,4,5-trimethoxy-, hemisulfate	752			752		752			
	Pheniprazine HCl, see: Hydrazine, (alpha-methylphenethyl)-, hydrochloride	502								
B	Phenobarbital, see: Barbituric acid, 5-ethyl-5-phenyl-	137								
	Phenol	753	753							753
	Phenol, p-(2-aminoethyl)-3-methoxy-	754			754					
	Phenol, m-(N-(2-imidazolin-2-ylmethyl)-p-toluidino)-, monoethanesulfonate (salt)	755								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>889	Phenol, 2,2'-methylenebis (3,4,6-trichloro)-	756-772	756 758 760 761 762 763 764 767 768 769 770 772	756 758 766 767	757 758 759 760 761 762 763 764 765 766 767 768 770 771		757 762 771		763	759 762 765 769
	Phenolphthalein	773		773						773
	Phenothiazine drugs (unspecified)	774								774
	Phenothiazine, 2-chloro-10-3(3-dimethyl-amino)propyl)-	775-777					777			
	Phenothiazine, 2-chloro-10-(3-(dimethyl-amino)propyl)-, mono-hydrochloride	778-779				779	779			
	Phenothiazine, 2-chloro-10-(3-(4-methyl-1-piperazinyl) propyl	780-781			780					780
	Phenothiazine, 10-(2-diethylamino)propyl)	782-783								782
	Phenothiazine, 10-(3-(dimethylamino) propyl)-, monohydrochloride	784-786			784					784
	Phenothiazine, 2-(ethylthio)-10-(3-(4-methyl-1-piperazinyl)propyl)-	787			787					787

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>689	Phenothiazine, 10-(3-(4-methyl-1-piperazinyl)propyl)-2-(trifluoromethyl)-	788-789	789		788 789					788
	Phenoxybenzamine, see: Benzylamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-	151								
	Phentolamine methane sulphonate, see: Phenol, m-(N-(2-Imidazolin-2-ylmethyl)-p-toluidino)-, monomethanesulfonate (salt)	755								
	Phenytoin, see: Hydantoin, 5,5-diphenyl-	472-487								
	Phisohex, see: Phenol, 2,2'-methylenebis (3,4,6-trichloro)-	756-772								
OP	Phorate, see: Phosphorodithioic acid, O,O-diethyl S-(ethylthio)methyl ester	920								
OP	3-Phosphabicyclo(4.4.0) decane, p-chloro-2,4-dioxa-5-methyl-p-thiono-	790			790					
OP	Phosphine oxide, tri-o-tolyl-	791								
OP	Phosphofluoridic acid, methyl-, isopropyl ester	792						792		
OP	Phospholipase A	793								
OP	Phosphonic acid, decyl-, ethyl p-nitrophenyl ester	794	794	794	794					
OP	Phosphonic acid, ethyl-, 2-chloroethyl 2,2-dichlorovinyl ester	795	795	795	795					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphonic acid, O-ethyl-O-(4-nitro-phenyl)-ethyl ester	796				796		796		
OP	Phosphonic acid, pentyl-, ethyl p-nitrophenyl ester	797	797	797	797					
OP	Phosphonic acid, 2-phenylethyl-, ethyl p-nitrophenyl ester	798	798	798	798					
OP	Phosphonic acid, phenylmethyl-, ethyl p-nitrophenyl ester	799	799	799	799					
OP	Phosphonic acid, 3-phenylpropyl-, ethyl p-nitrophenyl ester	800	800	800	800					
OP	Phosphonic acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester	801				801				801
OP	Phosphonodithioic acid, chloromethyl-S-(p-chlorophenyl)O-isopropyl ester	802			802					
OP	Phosphonodithioic acid, O-isopropyl-S-p-tolyl chloromethyl ester	803			803					
OP	Phosphonofluoridic acid, methyl-, isopropyl ester	804-805				804		805		
OP	Phosphonofluoridic acid, methyl-, 1,2,2-trimethyl propyl ester	806						806		
OP	Phosphonothioic acid, ethyl-, di(2-chloroethyl) ester	807	807	807	807					
OP	Phosphonothioic acid, ethyl-, O-ethyl O-(2,4,5-trichlorophenyl) ester	808-809	808	808	808 809					

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphonothioic acid, methyl-, 2,4-dichlorophenyl methyl ester	810	810	810	810					
OP CN	Phosphonothioic acid, phenyl, -O-ethyl ester, O-ester with p-hydroxybenzonitrile	811			811					
OP	Phosphonothioic acid, phenyl-, O-ethyl O-(p-nitrophenyl) ester	812			812					
OP	Phosphonothioic acid, O-ethyl S-(2-dimethyl amino ethyl)methyl ester	813						813		
OP	Phosphonotrithioic acid, S,S-dipropyl methyl	814			814					
OP	Phosphonotrithioic acid, methyl-, S-propyl-S-diethlsuccinate	815			815					
OP	Phosphoramidic acid, methyl-, 4-tert-butyl-2-chlorophenyl methyl ester	816-817			816 817			817		
OP	Phosphoramidothioic acid, isopropyl-, O-2,4-dichlorophenyl O-methyl ester	818			818			818		
Al	Phosphoric acid, aluminum salt	819	819							
OP	Phosphoric acid, bis(2-ethylhexyl) o-tolyl ester	820								
OP	Phosphoric acid, bis(p-ethylphenyl)ester	821			821					
OP	Phosphoric acid, bis(4-ethylphenyl) 2-propylphenyl ester	822			822					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphoric acid, bis(2-ethylphenyl) p-tolyl ester	823			823					
OP	Phosphoric acid, bis(o-propylphenyl) p-tolyl ester	824			824					
OP	Phosphoric acid, bis (3,5-xylyl) 2-ethylphenyl ester	825			825					
OP	Phosphoric acid, 2-chloro-1-(2,4-dibromophenyl) vinyl dimethyl ester	826						826		
OP	Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl ester	827			827					
OP	Phosphoric acid, 2-chloro-1-(2,4-dichlorophenyl) vinyl dimethyl ester	828						828		
OP	Phosphoric acid, 2-chloro-1-(2,5-dichlorophenyl) vinyl dimethyl ester	829						829		
OP	Phosphoric acid, 2-chloroethyl 2,2-dichlorovinyl methyl ester	830	830	830	830					
OP	Phosphoric acid, 2-chloroethyl 2-dichlorovinyl methyl ester	831			831			831		
OP	Phosphoric acid, 2-chloroethyl ethyl p-nitrophenyl ester	832	832	832	832					
OP	Phosphoric acid, o-chlorophenyl diphenyl ester	833								
OP	Phosphoric acid, 1-((p-chlorophenyl) thio) vinyl dimethyl ester	834			834					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphoric acid, 2-chloro-1-(2,4,5-trichloro-phenyl)vinyl dimethyl ester	835			835					
OP	Phosphoric acid, o-cresyl diphenyl ester	836	836	836	836					
OP	Phosphoric acid, cyclic methylene-o-phenylene o-tolyl ester	837-839	838 839	838	838 839					
OP	Phosphoric acid, 1,2-dibromo-2,2-dichloroethyl dimethyl ester	840				840				840
OP	Phosphoric acid, di(2-chloroethyl) 2,2-dichlorovinyl ester	841	841	841	841					
OP	Phosphoric acid, di(2-chloroethyl) p-nitrophenyl ester	842	842	842	842					
OP	Phosphoric acid, di(2-chloroethyl) 2,3,5-trichlorophenyl ester	843	843	843	843					
OP	Phosphoric acid, di-o-chlorophenyl phenyl ester	844								
OP	Phosphoric acid, 2-2-dichlorovinyl dimethyl ester	845	845	845	845					
OP	Phosphoric acid, diethyl p-nitrophenyl ester	846						846		
OP	Phosphoric acid, di(o-ethylphenyl) p-tolyl ester	847			847					
OP	Phosphoric acid, diethyl o-tolyl ester	848								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphoric acid, dimethyl (1-(dimethyl phosphonyl)vinyl) ester	849			849			849		
OP	Phosphoric acid, dimethyl ester, ester with (E)-3 hydroxy-N-methyl crotonamide	850			850					
OP	Phosphoric acid, diphenyl o-tolyl ester	851-853	851	851	851 852					
OP	Phosphoric acid, di-p-tolyl 2-ethyl phenyl ester	854			854					
OP	Phosphoric acid, di-p-tolyl o-ethyl phenyl ester	855			855					
OP	Phosphoric acid, di-o-tolyl m-tolyl ester	856			856					
OP	Phosphoric acid, di-p-tolyl o-tolyl ester	857			857					
OP	Phosphoric acid, di-o-tolyl p-tolyl ester	858			858					
OP	Phosphoric acid, di-p-tolyl o-tolyl ester	859			859					
OP	Phosphoric acid, di(3,5-xylyl) o-tolyl ester	860			860					
OP	Phosphoric acid, o-hydroxyphenyl phenyl ester	861	861	861	861					
OP	Phosphoric acid, tolyl ester	862			862					862
OP	Phosphoric acid, o-tolyl ester	863		863	863					863
OP	Phosphoric acid, triaryl ester	864			864					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphoric acid, tri(o-biphenylyl)ester	865								
OP	Phosphoric acid, tributyl ester	866			866					
OP	Phosphoric acid, triethyl ester	867								
OP	Phosphoric acid, tri-p-ethylphenyl ester	868-869		869	868 869					
OP	Phosphoric acid, tri-4-ethyl phenyl ester	870	870	870	870					
OP	Phosphoric acid, tri-o-ethyl phenyl ester	871								
OP	Phosphoric acid, triphenyl ester	872								
OP	Phosphoric acid, tritolyl ester	873-875	873 874	874 875	874 875					
OP	Phosphoric acid, tri-m-tolyl ester	876								
OP	Phosphoric acid, tri-o-tolyl ester	877-894	880 883 885 887 888 890 891 892 893	878 881 882 884 885 891 892 894	877 878 880 882 883 884 885 886 887 888 889 890 891 892			894		
OP	Phosphoric acid, tri-p-tolyl ester	895								
OP	Phosphoric acid, trixylyl ester	896			896					

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphoric acid, tri-2,4-xylyl ester	897								
OP	Phosphoric acid, tri-2,5-xylyl ester	898								
OP	Phosphoric acid, tri-2,6-xylyl ester	899								
OP	Phosphoric acid, tri-3,5-xylyl ester	900								
OP	Phosphorochloridic acid, di-o-tolyl ester	901								
OP	Phosphorochloridous acid, bis(3,5-xylyl) ester	902						902		902
OP	Phosphorodiamidic fluoride, N,N'-dibutyl-	903	903	903	903					
OP	Phosphorodichloridic acid, o-tolyl ester	904			904					
OP	Phosphorodithioic acid, S,S'-benzylidene bis-O,O-dimethyl	905			905					
OP	Phosphorodithioic acid, S,S'-benzylidene O,O,O',O'-tetramethyl ester	906			906					
OP	Phosphorodithioic acid, bis(4-chlorophenyl) methyl-O,O-diethyl	907			907					
OP	Phosphorodithioic acid, S-(p-chloro-phenyl)thio methyl O,O-diethyl ester	908			908					
OP	Phosphorodithioic acid, S-(((p-chloro-phenyl)thio)methyl) O,O'-diethyl ester	909			909					
OP	Phosphorodithioic acid, S-(((p-chloro-phenyl)thio)methyl)O,O-dimethyl ester	910-911			910 911			911		

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphorodithioic acid, S((4,6-diamino-S-triazin-2-yl)methyl)O,O-dimethyl ester	912			912					
OP	Phosphorodithioic acid, S-(((2,5-dichloro-phenyl)thio)methyl) O,O-diethyl ester	913			913					
OP	Phosphorodithioic acid, (((3,4-dichloro-phenyl)thio)methyl) O,O-diethyl ester	914			914					
OP	Phosphodithioic acid, S-((3,4-dichloro-phenyl)thio)methyl) O,O-dimethyl ester	915			915					
OP	Phosphorodithioic acid, O,O-diethyl ester, S,S-diester with p-dioxane-2,3-dithiol	916			916					
OP	Phosphorodithioic acid, O,O-diethyl ester, S-ester with 3-(mercaptomethyl)-1,2,3-benzotriazin-4(3H)one	917			917					
OP	Phosphorodithioic acid, O,O-diethyl S-(2 ethylthio)ethyl)ester	918-919			918 919			919		919
OP	Phosphorodithioic acid, O,O-diethyl S-(ethylthio)methyl ester	920			920					
OP	Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-(2-methoxyacetyl) acetamide	921			921					
OP	Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-methylacetamide	922			922			922		922

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphorodithioic acid, 0,0-dimethyl ester, S-ester with 3(mercaptomethyl)-1,2,3-benzotriazin-4(3H)-one	923-925			923 925			924		
OP	Phosphorodithioic acid, 0,0-dimethyl ester S-ester with N-(mercaptomethyl) phthalimide	926			926			926		
OP	Phosphorodithioic acid, 0-ethyl S,S-dipropyl ester	927			927					
OP	Phosphorodithioic acid, S,S'-methylene 0,0,0',0'-tetraethyl ester	928-929			928 929					928
OP	Phosphonodithioic acid, methyl-, 0-phenyl S-propyl ester	930			930					
OP	Phosphorofluoridic acid, bis(1-methylethyl) ester	931-932	932	932	931 932					
OP	Phosphorofluoridic acid, methyl-, isopropyl ester	933					933	933		933
OP	Phosphorothioic acid, 0-(2-(sec-butoxy-'methylthio)ethyl) 0,0-diethyl ester	934			934			934		
OP	Phosphorothioic acid, 0-(2-chloro-1-(2,4-dichlorophenyl)vinyl 0,0-dimethyl ester	935			935			935		
OP	Phosphorothioic acid, 0-(2-chloro-4-nitrophenyl) 0,0-dimethyl ester	936			936					
OP	Phosphorothioic acid, 0-(p-cyanophenyl) 0,0-dimethyl ester	937			937					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphorothioic acid, 0-(2,4-dichloro-phenyl)-0,0-diethyl ester	938			938					
OP	Phosphorothioic acid, 0,0-diethyl 0-(2-isopropyl-6-methyl-4-pyrimidinyl)ester	939					939			939
OP	Phosphorothioic acid, 0,0-diethyl-0-(4-(methylthio)-3,5-xylyl) ester	940			940					
OP	Phosphorothioic acid, 0,0-diethyl 0-(p-nitrophenyl) ester	941-943			941		943	942		943
OP	Phosphorothioic acid, 0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) ester	944-945			944 945					
OP	Phosphorothioic acid, 0,0-diethyl 0-1,2,2-trimethyl propyl ester	946			946			946		
OP	Phosphorothioic acid, 0,0-diisopropyl 0-(4-methylsulfinyl phenyl) ester	947			947			947		
OP	Phosphorothioic acid, 0,0-dimethyl ester, 0,0-diester with 4,4'-thiodiphenol	948			948					
OP	Phosphorothioic acid, 0,0-dimethyl S-(2-(ethylsulfinyl)ethyl) ester	949			949			949		
OP	Phosphorothioic acid, 0,0-dimethyl S-(2-(ethylsulfonyl) ethyl)ester	950						950		
OP	Phosphorothioic acid, 0,0-dimethyl S-(2-ethylthioethyl) ester	951						951		
OP	Phosphorothioic acid, 0,0-dimethyl S-(2-(isopropylsulfino) ethyl) ester	952						952		
OP	Phosphorothioic acid, 0,0-dimethyl 0-(p-methylsulfinyl)phenyl) ester	953			953			953		

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Phosphorothioic acid, 0,0-dimethyl-, 0-(4-methylthio)-m-tolyl) ester	954-955			955					
OP	Phosphorothioic acid, 0,0-dimethyl 0-(4-methylthio)-3,5-xylyl) ester	956			956					
OP	Phosphorothioic acid, 0,0-dimethyl-0-(p-nitrophenyl)ester	957			957					
OP	Phosphorothioic acid, 0,0-dimethyl 0-(4-nitro-m-tolyl) ester	958			958					
OP	Phosphorothioic acid, 0,0-dimethyl S-((4-oxo-1,2,3-benzotriazin-3(4H)-yl) methyl) ester	959						959		
OP	Phosphorothioic acid, 0-0-dimethyl 0 (2,4,5-trichlorophenyl) ester	960			960					
OP	Phosphorotrithioic acid, 0-methyl S,S-dipropyl ester	961			961					
OP	Phosphorotrithioic acid, S,S,S-tributyl ester	962			962					
OP	Phosphorotrithious acid, tributyl ester	963			963					
OP	Phosphorous acid, tri-o-tolyl ester	964			964					
	Phthalate plasticizers (mixture)	965			965		965			965
	Phthalimide, N-(2,6-dioxo-3-piperidyl)-	966-967	966 967						966 967	
OP	Phthalimide, N-hydroxy-, 0-ethyl 0-isopropyl phosphorothioate	968			968			968		

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Picolinic acid, 5-amino-6-(7-amino-5,8-dihydro-6-methoxy-5,8-dioxo-2-quinolyl-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methyl	969	969						969	
HZ	Picolinic acid, hydrazide	970			970					
	2-Picolinium, 1-((4-amino-2-propyl-5-pyrimidinyl)methyl)-, chloride, hydrochloride	971-972	971 972		971					
TP	Picrotoxin	973-975			974		973 974 975			
	Piperamide, see: Acetanilide, 4'-(4-(3-dimethylamino)propyl)-1-piperazinyl)-	5								
>10%	Piperazine	976								
	1-Piperazineethanol, 4-(3-(2-chloro-phenothiazin-10-yl)propyl)-	977								
	1-Piperazineethanol, 4-(3-(2-chloro-phenothiazin-10-yl)propyl)-,heptanoate	978								
	2-Piperidine acetic acid, alpha-phenyl-, methyl ester hydrochloride	979								
	Piperidine, 2-chloroethyl-, hydrochloride	980	980		980					
	2-Piperidineethanol, alpha, alpha-diphenyl-1-methyl-hydrochloride	981								981
	1-piperidine propanol, alpha-cyclohexyl alpha-phenyl-, hydrochloride	982								982

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	1-Piperidine propanol, alpha-cyclopentyl-alpha-phenyl-	983								983
	3-Piperidinol, 1-methyl-, citrate	984								984
	Plasmocide, see: Quinoline, 8-((4-diethyl-amino)-1-methylbutyl)amino)-6-methoxy-	1041								
Pb	Plumbane, tetraethyl-	985-987	987		985 986					
Hg	PMC, see: Mercury, chlorophenyl	657								
	Pregn-4-ene-3,20-dione, 17,21-dihydroxy-, succinate, sodium salt	988			988		988			
	Primidone, see: 4,6(1H,5H)-Pyrimidine-dione, 5-ethyldihydro-5-phenyl-	1025								
	Procainamide, see: Benzamide, p-amino-n-2-(diethyl(amino)ethyl))-	138								
	Procaine, see: Benzoic acid, p-amino, 2-(diethylamino)ethyl ester	146								
	Procarbazine, see: p-Toluamide, N-isopropyl-alpha-(2-methylhydrazino)-	1188-1189								
	Prochlorperazine, see: Phenothiazine, 2-chloro-10-(3-(4-methyl-1-piper-azinyl)propyl-	730-731								
OP	Prolate, see: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with N-(mercaptomethyl) phthalimide	926								

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Proline, 5-oxo-	989					989			
	Promazine HCl, see: Phenothiazine, 10-(3-(dimethylamino)propyl)-, monohydrochloride	784-786								
	Pronethalol HCl, see: Naphthalene methanol, alpha-(isopropylamino) methyl-, hydrochloride	709								
	1,2-Propanediol, dinitrate	990				990				990
C	1,3-Propanediol, 2-methyl-2-propyl-, dicarbamate	991					991			991
	Propanol, see: Propyl alcohol	1004								
CN	1-Propene-1,1,3-tricarbonitrile, 2-amino-	992				992				
OP	Propionic acid, 2-amino-3-hydroxy-, phosphonate, (ester)	993								
	Propionic acid, 2-amino-3-sulfino-, L-	994					994			
	Propionic acid, beta-N-oxalyl-L-alpha, beta-diamino-	995-996			995 996					
CN	Propionitrile, 3-diamino-	997			997					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
CN	Propionitrile, 3,3'-iminodi-	998-1003	998 999 1000 1001		998 999 1000 1001 1002		1002			
	Propoxyphene hydrochloride, see: 2-Butanol, 4-(dimethylamino)-3-methyl-1,2-diphenyl-, propionate (ester), hydrochloride (+)-,	171-172								
	Propyl alcohol	1004								
	Propylamine	1005					1005			
TE	Pseudomona tabaci exotoxin	1006			1006					
	Psilocin, see: Indol-4-OL, 3(2-(dimethyl amino)ethyl)-	532								
OP	Psilocybin, see: Indol-4-OL,3-2-(dimethyl amino)ethyl)-, dihydrogen phosphate	533-534								
	Puromycin, see: Adenosine, 3'-(alpha-amino-p-methoxy hydrocennamamido)-3'-deoxy-N,N-dimethyl	61-62								
	Pyramat, see: Carbamic acid, dimethyl-6-methyl-2-propyl-4-pyrinidnyl ester	191								
	3-Pyridenecarboxamide, 6-amino-	1007-1010	1007 1008 1009 1010	1010	1010				1007 1008 1009	

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
>C5<	Pyridine, 2-((2-(dimethylamino)ethyl)(p-methoxybenzyl)amino)-, maleate (1:1)	1011								
	3-Pyridinemethanol, 5-hydroxy-4,6-dimethyl-, hydrochloride	1012			1012		1012			
	Pyridinium, 2-formyl-1-methyl-, chloride, oxime	1013			1013					
	Pyridinium, 2-formyl-1-methyl-, methanesulfonate, oxime	1014			1014					
	9H-Pyrido-(3,4-b)indole, 4,9-dihydro-7-methoxy-1-methyl-	1015				1015				1015
	9H-Pyrido(3,4-b)indole, -7-methoxy-1-methyl-	1016				1016				1016
	9H-Pyrido(3,4-b) indole, 7-methoxy-1-methyl-, hydrochloride	1017			1017		1017			
	9H-Pyrido(3,4-b)indole, 1,2,3,4-tetrahydro-7-methoxy-1-methyl	1018				1018				1018
	9H-Pyrido(3,4-b)indole, 1,2,3,4-tetrahydro-2-methyl-	1019				1019				1019
	9H-Pyrido(3,4-b)indol-7-ol, 1-methyl-	1020				1020				1020
	Pyridoxol hydrochloride	1021		1021			1021			
	Pyridoxol, methoxy-	1022	1022		1022		1022			
	4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-5-fluoro-	1023-1024	1023 1024		1023				1024	

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	4,6(1H,5H)-Pyrimidinedione, 5-ethyldi-hydro-5-phenyl	1025			1025					1025
	Pyrocatechol, 4-(2-aminoethyl)-5-hydroxy-	1026-1028	1027							
	Pyroglutamic acid, see: Proline, 5-oxo-	989								
OP	Pyrophosphoric acid, tetraethyl ester	1029				1029				1029
	Pyrrole, 2,4-dimethyl-3-ethyl-	1030			1030		1030			
	3-Pyrrolidine acetic acid, 2-carboxy-4-isopropenyl	1031	1031		1031					
>90Z	Pyrrolidine, 1,1-(2-butynylene) di-	1032-1033			1032 1033					
	1-Pyrrolidine propanol, alpha-cyclohexyl-alpha-phenyl-	1034								1034
	4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036			1035 1036					1035 1036
TP	Quinine chloride, see: Quinine, mono-hydrochloride	1037								
TP	Quinine, monohydrochloride	1037			1037					1037
TP	Quinine muriate, see: Quinine, mono-hydrochloride	1037								
	Quinolines, 8-amino- (not specified)	1038	1038		1038					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Quinoline, 7-chloro-4-(4-diethylamino-1-methyl-butylamino)-diphosphate	1039	1039	1039						
	Quinoline, 7-chloro-4((4-(diethyl amino)-1-methylbutyl)amino)-	1040	1040							
>207	Quinoline, 8-((4-diethylamino)-1-methyl-butyl) amino)-6-methoxy-	1041	1041							
	Quinoline, 6-methoxy-8-(3-diethylamino-propylamino)-	1042	1042							
	8-Quinolinol	1043			1043					
	8-Quinolinol, 5-chloro-3'-hydroxy-2'-naphthoate	1044			1044					
Cu	8-Quinolinol, 5-chloro-3'-hydroxy-2'-napthalate, copper (II) chelate	1045			1045					
	8-Quinolinol, 5-chloro-7-iodo-	1046-1051	1048 1049 1050 1051	1048 1050	1046 1048 1049 1050 1051	1047				1046 1047 1051
Cu	8-Quinolinol, copper (II) chelate	1052			1052					
	8-Quinolinol, 4,5'-dichloro-3'-hydroxy-2'-napthoate	1053			1053					
Cu	8-Quinolinol, 5-iodo-4'-chloro-3'-hydroxy-2'-napthoate, copper (II) chelate	1054			1054					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Cu	8-Quinolinolium 7'-bromo'3'hydroxy'2'-naphthoate, copper (II) chelate	1055			1055					
	8-Quinolinolium 4',7'-dibromo-3'-hydroxy-2'-naphthoate	1056			1056					
Cu	8-Quinolinolium 4',7'-dibromo-3'-hydroxy-2'-naphthoate, copper (II) chelate	1057			1057					
	8-Quinolinolium 1'-hydroxy-2'-naphthoate	1058			1058					
	8-Quinolinolium 3'-hydroxy-2'-naphthoate	1059			1059					
Cu	8-Quinolinolium 1'-hydroxy-2'-naphthoate, copper (II) chelate	1060			1060					
Cu	8-Quinolinolium 3'-hydroxy-2'-naphthoate, copper (II) chelate	1061			1061					
	8-Quinolinolium salicylate	1062			1062					
Cu	8-Quinolinolium salicylate, copper (II) chelate	1063			1063					
	Reserpine, see: 3-beta,20-alpha-Yohimban-16-beta-carboxylic acid, 18-beta-hydroxy-11,17-alpha-dimethoxy-, methyl ester, 3,4,5-trimethoxybenzoate (ester)	1229								
OP	Reserpine phosphate	1064					1064			
	Resorcinol, 2-p-mentha-1,8-dien-3-yl-5-pentyl-	1065-1066				1065 1066				

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Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Retinol, all trans-	1067-1068	1067 1068						1067 1068	
	Revonal, see: 4(3H)-Quinazolinone, 2-methyl-3-o-tolyl-	1035-1036								
OP	Ronnel, see: Phosphorothioic acid, O-O-dimethyl O(2,4,5-trichlorophenyl) ester	960								
OP	Ruelene, see: Phosphoramidic acid, methyl-, 4-tert-butyl-2-chlorophenyl methyl ester	816-817								
	Salicylic acid, monsodium salt	1069	1069							1069
OP	Sarin, see: Phosphonofluoridic acid, methyl-, isopropyl ester	804-805								
	Sarodormin, see: Gluterimide, 2-ethyl-2-phenyl-	436-438								
	Saxitoxin	1070-1071					1071			
TP	Scopolamine	1072								1072
TP	Scopolamine bromide	1073			1073		1073			
B	Secobarbital, see: Barbituric acid, 5-allyl-5-(1-methylbutyl)	131								
B	Seconal, see: Barbituric acid, 5-allyl-5-(1-methylbutyl)-	131								
	Semicarbazide	1074			1074					
	Semicarbazide, 4,4-diethyl-, hydrochloride	1075			1075					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Semicarbazide, thio-	1076-1077			1076 1077					
	Semioxamazide	1078			1078					
	Senna	1079								1079
OP	Serine, dihydrogen phosphate (ester), L-	1080					1080			
C	Sevin, see: Carbamic acid, methyl-, 1-naphthyl ester	200-201								
TB	Shigella Shigae toxin	1081								
	Sodium azide	1082 1083	1082 1083		1082					
B	Sodium methohexital, see: Barbituric acid, 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)-, sodium salt	132								
B	Sodium pentobarbital, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-, sodium salt	134-135								
B	Sodium pentothal, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-2-thio-, sodium salt	136								
B	Sodium thiopental, see: Barbituric acid, 5-ethyl-5-(1-methylbutyl)-2-thio-, sodium salt	136								
Sn	Stannane, acetoxytriphenyl-	1084								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Sn	Stannane, chlorotriethyl-	1085			1085					
Sn	Stannane, dibutyloxo-	1086								
Sn	Stannane, hydroxytriethyl-	1087	1087		1087					
Sn	Stannane, hydroxytriphenyl-	1088			1088					
Sn	Stannane, triethyl-	1089-1093	1089 1090 1092 1093		1092 1093					
	Streptonigrin, see: Picolinic acid, 5-amino-6-(7-amino-5,8-dihydro-6-methoxy-5,8-dioxo-2-quinolyl)-4-(2-hydroxy-3,4-dimethoxyphenyl)-3-methyl	969								
TP	Strychnine	1094-1095								
TP	Strychnine, sulfate (2:1)	1096-1097	1096		1096 1097		1097			
	Succinamic acid, alpha-amino-, L-	1098-1099					1098			
	Succinic acid	1100					1100			
	Succinic acid, 2-aminomethyl-, DL-	1101					1101			
	Succinic acid, 2,3-diamino-, meso-	1102					1102			
	Succinic acid, mercapto-, diethyl ester, S-ester with 0,0-dimethyl phosphorodithioate	1103-1106			1103 1104		1106	1105		1106

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholinesterase Inhibition	Effects in Offspring	Reported Human Incidence
	Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-	1107-1111	1107 1108 1110		1108 1109 1110 1111					
	TED, see: 1,4-Diazabicyclo(2.2.2)octane	262								
Te	Tellurium	1112-1113	1112	1113	1113				1112	
Te	Tellurium tetrachloride	1114	1114							
OP	TEPP, see: Pyrophosphoric acid, tetraethyl ester	1029								
TB	Tetanus toxin	1115-1116			1115		1116			
Sn	TETH, see: Stannane, hydroxytriethyl-	1087								
Pb	Tetraethyl lead, see: Plumbane, tetraethyl-	985-987								
	delta(Sup1)Tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-	278-284								
	delta(Sup8)-Tetrahydrocannabinol, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-	276-277								
	delta(Sup9)-Tetrahydrocannabinol, see: 6H-dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-	278-284								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	5H-Tetrazoloazepine, 6,7,8,9-tetrahydro-	1117-1122			1118 1119 1120 1121	1120 1122	1119 1122			
TA	Tetrodotoxin	1123-1125					1124 1125			
	Thalidomide, see: Phthalimide, N-(2,6-dioxo-3-piperidyl)-	966-967								
TI	Thallium	1126-1127	1126	1126 1127	1126					1127
TI	Thallium sulfate	1128-1129		1129	1128					1128
	delta(Sup8)THC, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-	276-277								
	delta(Sup9)THC, see: 6H-Dibenzo(b,d)pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)	278-284								
TP	Theobromine, 1-allyl-	1130			1130					
TP	Theobromine, 1-(2-butenyl)-	1131			1131					
TP	Theobromine, 1-ethyl-	1132			1132					
TP	Theobromine, 1-(2'-methoxyethyl)-	1133			1133					
TP	Theobromine, 1-(2'-methylallyl-)	1134			1134					
TP	Theobromine, 1-propyl	1135			1135					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
714	4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-	1136-1138			1136 1137		1137 1138			1136 1137
	4-Thia-1-azabicyclo(3.2.0) heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, monopotassium and monosodium salts	1139	1139		1139					
	4H-Thieno(2,3-b)(1,4)benzothiazine	1140			1140					
	9H-Thieno(3,4-b)(1,4)benzothiazine	1141			1141					
	9H-Thieno(3,2-b)(1,4)benzothiazine, 9-acetyl-	1142			1142					
	9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde	1143			1143					
	4H-Thieno(2,3-b)(1,4)benzothiazine-4-carboxaldehyde, 6-chloro	1144			1144					
	9H-Thieno(3,2-b)(1,4)benzothiazine-9-carboxaldehyde, 7-chloro	1145			1145					
	9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde, 7-chloro	1146			1146					
	4H-Thieno(2,3-b)(1,4)benzothiazine-4-carboxaldehyde, 6-(trifluoromethyl)-	1147			1147					
	9H-Thieno(3,2-b)(1,4)benzothiazine-9-carboxaldehyde, 7-(trifluoromethyl)-	1148			1148					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
215	9H-Thieno(3,4-b)(1,4)benzothiazine-9-carboxaldehyde, 7(trifluoromethyl)-	1149			1149					
	4H-Thieno(2,3-b)(1,4)benzothiazine, 6-chloro-	1150			1150					
	9H-Thieno(3,2-b)(1,4)benzothiazine, 7-chloro-	1151			1151					
	9H-Thieno(3,4-b)(1,4)benzothiazine, 7-chloro	1152			1152					
	4H-Thieno(2,3-b)(1,4)benzothiazine, 7-chloro-4-(3-dimethylaminopropyl)-, hydrochloride	1153			1153					
	9H-Thieno(3,4-b)(1,4)benzothiazine, 7-chloro-9-(3-dimethylaminopropyl)-, hydrochloride	1154			1154					
	9H-Thieno(3,4-b)(1,4)benzothiazine, 9-(3-dimethylaminopropyl)-, hydrochloride	1155			1155					
	9H-Thieno(3,4-b)(1,4)benzothiazine, 4-(3-dimethylaminopropyl)-6-(trifluoromethyl)-, hydrochloride	1156			1156					
	9H-Thieno(3,4-b)(1,4)benzothiazine, 9-(3-dimethylaminopropyl)-7-(trifluoromethyl)-, hydrochloride	1157			1157					
	4H-Thieno(2,3-b)(1,4)benzothiazine, 6-(trifluoromethyl)-	1158			1158					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	9H-Thieno(3,2-b)(1,4) benzothiazine, 7-(trifluoromethyl)-	1159			1159					
	9H-Thieno(3,4-b)(1,4) benzothiazine, 7-(trifluoromethyl)-	1160			1160					
	Thiethylperazine, see: Phenothiazine, 2-(ethylthio)-10-(3-(4-methyl-1-piperazinyl)propyl)-	787								
OP	Thiocron, see: Phosphorodithioic acid, O,O-dimethyl ester, S-ester with 2-mercapto-N-(2-methoxyacetyl)acetamide	921								
	Thiophene, 3-(2-amino-4-chlorophenyl)thio-	1161			1161					
	Thiophene, 2-(2-amino-4-chlorophenyl)thio-3-bromo-	1162			1162					
	Thiophene, 3-(2-amino-4-chlorophenyl)thio-4-bromo	1163			1163					
	Thiophene, 3-(2-aminophenyl) thio-	1164			1164					
	Thiophene, 2-(2-aminophenyl)thio-3-bromo-	1165			1165					
	Thiophene, 3-(2-aminophenyl)thio-4-bromo-	1166			1166					
	Thiophene, 3-((2-amino(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-	1167			1167					
	Thiophene, 2-((2-amino-(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-3-bromo-	1168			1168					
	Thiophene, 3-((2-amino(alpha, alpha, alpha-trifluoro-p-tolyl)))thio-4-bromo-	1169			1169					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Thiophene 3-bromo-2-(4-chloro-2-nitrc phenyl)thio-	1170			1170					
	Thiophene, 3-bromo-4-(4-chloro-2-nitro-phenyl)thio-	1171			1171					
	Thiophene, 3-bromo-2-(2-nitrophenyl)thio-	1172			1172					
	Thiophene, 3-bromo-4-(2-nitrophenylthio)-	1173			1173					
	Thiophene, 3-bromo-2-((2-nitro-(alpha, alpha, alpha-trifluoro-p-tolyl)thio)-	1174			1174					
	Thiophene, 3-bromo-4-((2-nitro-(alpha, alpha, alpha-trifluoro-p-tolyl)thio)-	1175			1175					
	Thiophene, 3-(4-chloro-2-nitrophenyl)thio-	1176			1176					
HZ	Thiophene hydrazide	1177			1177					
	Thiophene, 3-(2-nitrophenylthio)-	1178			1178					
	Thiophene, 3-(2-nitro-alpha, alpha, alpha-trifluoro-p-tolyl)thio-	1179			1179					
OP	Thiopyrophosphoric acid, tetrapropyl ester	1180			1180			1180		
	Thioxanthene-delta(sup9)gamma-propylamine, 2-chloro-N,N-dimethyl, hydrochloride	1181								
Sn	Tin, dioctyl-, acetate	1182								
Sn	Tin, triethyl-, sulphate	1183-1186	1183 1185 1186	1184	1183 1186					

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
Sn	Tin, trioctyl-, dilaurate	1187								
	TMBDA, see: 1,3-Butanediamine, N,N,N',N'-tetramethyl-	169								
OP	TOCP, see: Phosphoric acid, tri-o-tolyl ester	876-895								
	Tolazoline HCl, see: 2-Imidazoline, 2-bentyl-hydrochloride	513								
	p-Toluamide, N-isopropyl-alpha-(2-methylhydrazino)	1188-1189	1188				1189		1188	
	Toluene	1190-1191			1190 1191		1191			1190 1191
	Transamine sulfate, see: Cyclopropylamine 2-phenyl-, sulfate, trans-(+,-)-,(2:1)	256								
	Tranylcypromine sulfate, see: Cyclopropylamine, 2-phenyl-, sulfate, trans-(+,-)-, (2:1)	256								
	Tremorine, see: Pyrrolidine, 1,1-(2-butynylene) di-	1032-1033								
	Triazoic acid, see: Hydrazoic acid	504								
	Tributyltin oxide, see: Distannoxane, hexabutyl-	296								
OP	Trichlorfon, see: Phosphonic acid, (2,2,2-trichloro-1-hydroxyethyl)-, dimethyl ester	801								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
OP	Trichloronate, see: Phosphonothioic acid, ethyl-,O-ethyl O-(2,4,5-trichlorophenyl) ester	808-809								
OP	Tri-o-cresyl phosphate, see: Phosphoric acid, tri-o-tolyl ester	876-895								
CN	Tricyanoaminopropene, see: 1-Propene-1,1,3-tricarbonitrile, 2-amino-	992								
	Triethylcholine	1192						1192		
	Triethylenediamine, see: 1,4-Diazabicyclo(2.2.2) octane	262								
Sn	Triethyltin, see: Stannane, triethyl-	1089-1093								
Sn	Triethyltin hydroxide, see: Stannane, hydroxytriethyl-	1087								
	Trifluoperazine, see: Phenothiazine, 10-(3-(4-methyl-1-piperazinyl)propyl)-2-(trifluoromethyl)-	788-789								
	Triparanol, see: Ethanol, 2-(p-chlorophenyl)-1-(p-(2-(diethylamino)ethoxy) phenyl)-1-p-tolyl-	324								
Sn	Triphenyltin acetate, see: Stannane, acetoxytriphenyl-	1084								
Sn	Triphenyltin hydroxide, see: Stannane, hydroxytriphenyl-	1088								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
720<	1-alpha-H,5-alpha-H-Tropane-2-beta-carboxylic acid, 3-beta-hydroxy-methyl ester, benzoate (ester) hydrochloride	1193								
	1-alpha-H,5-alpha-H-Tropane, 3-alpha-(diphenyl methoxy)	1194								1194
	Tropanium, 3-alpha-hydroxy-9-methyl, p-tolylacetate	1195								
	Tropanol aryl esters (unspecified)	1196								
	Tropilidene, see: 1,3,5-Cycloheptatriene	250								
	Tropine, and aryl esters (unspecified)	1197			1197		1197			
	2-d-Tropine, p-nitrophenylacetate (ester)	1198					1198			
	2-alpha-Tropine, p-tolylacetate (ester)	1199					1199			
	Turpentine	1200			1200		1200			
	o-Tyrosine, DL-	1201					1201			
	Uracil, 5-fluoro	1202-1205	1202 1204 1205		1202 1205				1204	1203 1205
	Urea, ((p-bromophenyl)acetyl)-	1206-1207		1207	1206					
	Urea, ethyl nitroso-	1208-1214	1208 1209 1210 1211 1212 1213 1214	1208 1214					1210 1212 1213 1214	

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
	Urea, hydroxy-	1215	1215						1215	
	Urea, methyl nitroso-	1216-1217	1216 1217	1217						
	Urea, (2-phenylbutyryl)-	1218			1218					1218
	Urease	1219	1219		1219					
C	Urethane, see: Carbamic acid, ethyl ester	190								
	Uridine, 2'-deoxy-5-fluoro	1220-1221	1220 1221						1220 1221	
	Valeric acid, 2-amino-5-sulfo-, DL-	1222					1222			
	Valeric acid, 2,2-diphenyl-, 2-(diethyl-amino) ethyl ester	1223			1223		1223			
	Valium, see: 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-	144								
TP	Veratrum alkaloids (Unspecified)	1224			1224					1224
TP	Vinblastine, see: Vincaleukoblastine	1225								
TP	Vinblastine sulfate, see: Vincaleuko-blastine, sulfate (1:1) (salt)	1226								
TP	Vincaleukoblastine	1225		1225	1225					1225
TP	Vincaleukoblastine, sulfate (1:1) (salt)	1226		1226						
TP	Vincristine, see: Leurocristine	589-598								

Chemical Class Codes	Chemical Name	Pages	CNS Structural Damage	PNS Structural Damage	Gross Dysfunction	Performance Dysfunction	Instrument Detectable Dysfunction	Cholin-esterase Inhibition	Effects in Offspring	Reported Human Incidence
TP	Vincristine sulfate, see: Leurocristine, sulfate (1:1) (salt)	599-604								
	Vitamin A, see: Retinol, all trans-	1067-1068								
	Xylitol	1227	1227							1227
	Yohimbam-16-alpha-carboxylic acid, 17-alpha-hydroxy-, methyl ester	1228			1228		1228			
	3-beta,20-alpha-Yohimban-16-beta-carboxylic acid, 18-beta-hydroxy-11,17-alpha-dimethoxy-, methyl ester, 3,4,5-trimethoxybenzoate (ester)	1229			1229					
	Yohimbine, see: Yohimbam-16-alpha-carboxylic acid, 17-alpha-hydroxy-, methyl ester	1228								
C	Zectran, see: Carbamic acid, methyl-, 4-dimethyl-amino-3,5-xylyl ester	198								
	Zoxazolamine, see: Benzoxazole, 2-amino-5-chloro-	148								
OP	Zytron, see: Phosphoramidothioic acid, isopropyl-, O-2,4-dichlorophenyl O-methyl ester	818								

Appendix: information sources.

Primary Journals

	Years	Volumes
Acta Neuropathol	1961-1975	1-33
Acta Pharm et Tox	1970-1975	28-37
Amer J Pathol	1970-1975	58-81
Arch Environ Health	1970-1975	20-30
Arch Neurol	1960-1975	3-32
Arch Pathol	1965-1969	79-88
Arch Toxicology	1973-1975	31-34
Biochem Pharmacol	1964-1975	13-24
Brain	1960-1975	83-98
Brain and Nerve	1970	22
Brain Research	1975	83-100
Brit J Indust Med	1970-1975	27-32
British J Pharm	1960-1975	15-55
Can J Comp Med	1973-1975	37-39
Can Med Assoc J	1974-1975	110-113
Comparative & General Pharm	1970-1974	1-5
Crit Rev Toxicol	1971-1974	1-3
Diseases of the Nervous System	1965-1975	8-36
Economic Botany	1960-1975	14-29
Environ Health Perspect	1972-1975	1-12
Experimental Brain Research	1966-1975	1-24
Experimental Neurology	1959-1975	1-49
European J of Toxicology	1969-1975	
Food and Cosmetic Toxicology	1963-1975	1-13
Internation J of Neuropharm	1962-1969	1-8
Int Rev Exp Pathol	1964-1975	3-14
Int Rev Neurobicl	1965-1975	8-18
Japanese J Pharm	1959-1975	8-25
John Hopkins Medical J	1970-1975	126-137
J Cell Biology	1971-1975	48-67
J Clinical Pathology	1960-1975	13-28
J Clinical Pharm	1970-1975	10-15
J Comp Neurol	1960-1975	114-164

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	Years	Volumes
J Comp Phys Psychology	1973-1975	84-89
J Economic Entomology	1967-1975	60-68
J Medicinal Chem	1974-1975	17-18
J Neurochem	1965-1975	12-25
J Neuropath Exp. Neurol	1960-1975	19-34
J Neurol Neurosurg Psychiatry	1960-1975	17-38
J Neurol Sci	1970-1975	13-24
J Occup Med	1970-1975	12-17
J Pathol	1970-1975	100-117
J Pharmacol Exp Ther	1970-1975	170-195
Lab Invest	1970-1975	22-33
Life Sci	1970-1975	9-17
New Eng J Med	1974	290-291
Neurology	1951-1975	1-25
Neuropharm	1970-1975	9-14
Pharmacology Biochem. Beh.	1973-1975	1-3
Practitioner	1973-1975	210-215
Proceedings R. Soc. Med	1970-1975	63-68
Psychopharmacologia	1971-1975	19-45
Res Comm Chem Path Phar	1970-1975	1-12
Res Vet Science	1970-1974	13-17
Pharmacol Toxicol	1967-1970	30-33
Science	1970-1972	167-178
Teratology	1969-1975	2-12
Toxicology	1973-1975	1-5
Toxicol & Appl Pharmacol	1962-1975	4-34
World Neurol	1960-1962	1-3
Secondary Sources		
Chemical Abstracts	1950-1975	44-83
Biological Abstracts	1950-1975	24-60
Excerpta Medica, Neuri & Neurosurg	1970-1975	24-31
TOXLINE		
MEDLINE		
Physicians Desk Reference		
Registry of Toxic Effects of Chemical Substances		
PHS-149 A Survey of Compounds Which Have Been Tested for Carcinogenicity		

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